2

Multicompartment Models

Most drugs entering the systemic circulation require a finite time to distribute fully throughout the available body space. This fact is particularly obvious upon rapid intravenous injection. During this distributive phase, drug concentration in the plasma will decrease more rapidly than in the postdistributive phase. Whether or not such a distributive phase is apparent depends on the frequency with which blood samples are taken. A distributive phase may last for only a few minutes, for hours, or even for days.

If drug distribution is related to blood flow, highly perfused organs and tissues such as the liver and kidney should be in rapid distribution equilibrium with the blood. The blood and all readily accessible fluids and tissues may often be treated kinetically as a common homogeneous unit generally referred to as the central compartment. As discussed in Chap. 1 with respect to the one-compartment model, kinetic homogeneity does not necessarily mean that the drug concentrations in all tissues of the central compartment at any given time are the same. However, it does assume that any change that occurs in the plasma level of a drug quantitatively reflects a change that occurs in central compartment tissue levels.

Following the intravenous injection of a drug that exhibits multicompartment pharmacokinetics, the levels of drug in all tissues and fluids associated with the central compartment should decline more rapidly during the distributive phase than during the postdistributive phase (Fig. 2.1). In contrast, drug levels in poorly perfused tissues (e.g., muscle, lean tissue, and fat) first increase, reach a maximum, and then begin to decline during the distributive phase (Fig. 2.2). After some time, a pseudodistribution equilibrium is attained between the tissues and fluids of the central compartment and the poorly perfused or less readily accessible tissues. Once pseudodistribution equilibrium has been established, loss of drug from the plasma is described by a monoexponential process indicating kinetic homogeneity with respect to drug levels in all fluids and tissues of the body. The

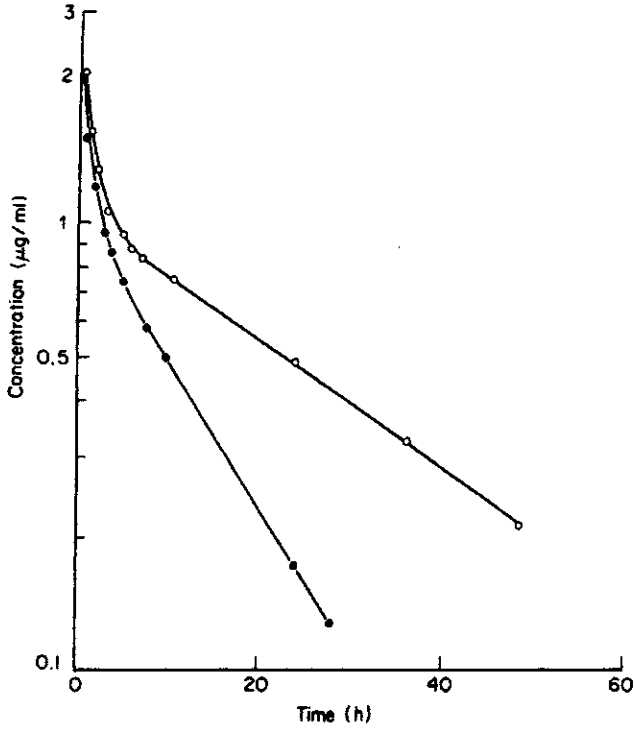


Fig. 2.1 Multiexponential decline of griseofulvin concentration in plasma following intravenous administration of the drug to two healthy volunteers. (Data from Ref. 1.)

access of drug to the various poorly perfused tissues may occur at different rates. Frequently, however, for a given drug these rates would appear to be very similar and, therefore, cannot be differentiated based solely on plasma concentration-time data. Consequently, all poorly perfused tissues are often "lumped" into a single peripheral compartment. It must be realized however, that the time course of drug levels in a hypothetical peripheral compartment, as inferred from the mathematical analysis of plasma concentration data, may not exactly correspond to the actual time course of drug levels in any real tissue. The peripheral compartments of pharmacokinetic models are, at best, hybrids of several functional physiologic units.

The particular compartment (i.e., central or peripheral) with which some tissue or part of a tissue may be associated often depends on the properties of the particular drug being studied. For example, the brain is a highly perfused organ. However, it is clearly separated from the blood by an apparent barrier with lipid characteristics. There-

fore, for lipid-soluble drugs the brain would probably be in the central compartment, whereas for more polar drugs the brain would probably be considered as part of a peripheral compartment. Hence, depending on the drug, the brain may be in the peripheral or in the central compartment.

As with the one-compartment model, drug elimination in multicompartment systems is assumed to occur in a first-order fashion. Transfer of drug between body compartments is also assumed to occur by first-order processes.

Following intravenous injection many drugs require more than one exponential term to characterize the resulting decline in plasma concentrations as a function of time. The number of exponentials needed to

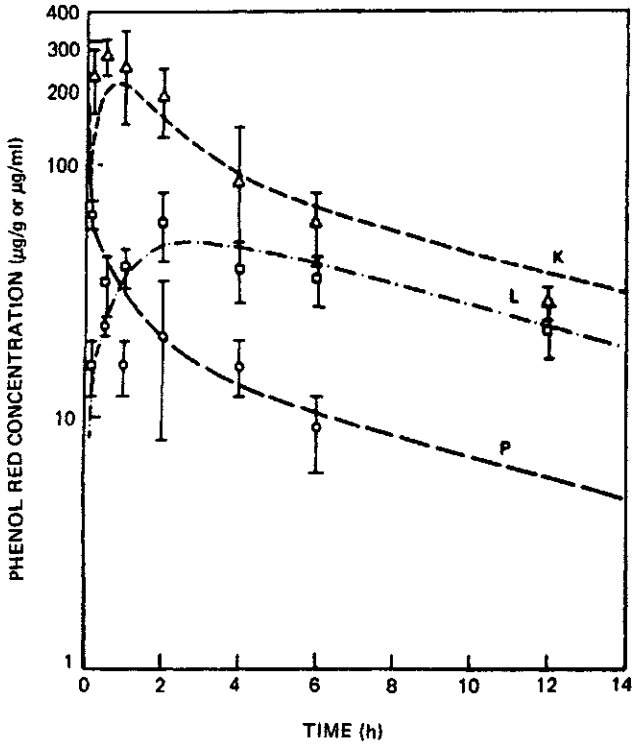


Fig. 2.2 Time course of tissue and plasma concentrations of phenol red in the dogfish shark after intravenous injection of the compound. Phenol red is so polar that even highly perfused organs such as the kidney and liver take on the characteristics of a peripheral compartment. △ kidney, □ liver, ○ plasma. (From Ref. 2 © 1976 Plenum Publishing Corp.)

describe adequately such a plasma concentration versus time curve determines the number of kinetically "homogeneous" compartments that a drug confers on the body. There are several types of n-compartment systems for any n-exponential curve. They differ in that elimination may be assumed to occur either from the central compartment, from one of the peripheral compartments, or from any combination of the central or peripheral compartments. Therefore, there are three types of two-compartment models and seven types of three-compartment models which are mathematically indistinguishable on the basis of the usually available experimental data (drug concentrations in the plasma and/or urinary excretion data). In the absence of information to the contrary, it is usually assumed that drug elimination takes place exclusively from the central compartment. All subsequent equations are based on this assumption unless otherwise stated. The basis of this assumption is that the major sites of biotransformation and excretion (i.e., the liver and kidneys) are well perfused with blood and are therefore presumed to be rapidly accessible to drug in the systemic circulation.

INTRAVENOUS INJECTION

Drug Concentrations in the Plasma

Following the rapid intravenous injection of a drug that distributes in the body according to an n-compartment system with elimination occurring from the central compartment, the disposition function for the central compartment $d_{s,c}$ is given by (see Appendix B)

$$d_{s,c} = \frac{\prod_{i=2}^{n} (s + E_i)}{\prod_{i=1}^{n} (s + \lambda_i)} \tag{2.1}$$

where n is the number of driving force compartments (i.e., compartments having exit rate constants), s is the Laplace operator, E_i is the sum of the exit rate constants from the ith compartment (e.g., $E_1 = k_{10} + k_{12}$ and $E_2 = k_{21}$ in Fig. 2.3), and λ_i is a disposition rate constant which may be expressed in terms of the individual intercompartmental transfer rate constants and elimination rate constants. When a drug is administered as an intravenous bolus, the input function in_s is

$$in_s = X_0 \tag{2.2}$$

where X_0 is the intravenous dose. The Laplace transform for the amount of drug in the central compartment $a_{s,c}$ is given by the product

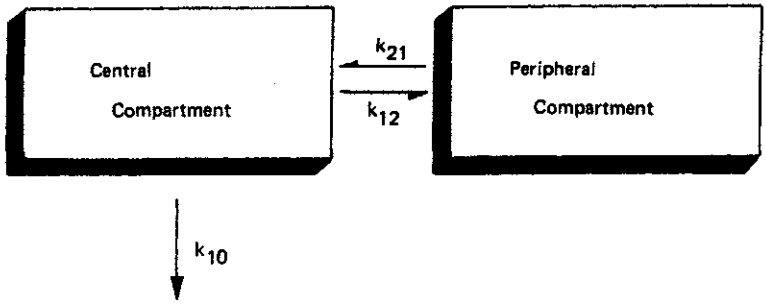


Fig. 2.3 Schematic representation of the body as a two-compartment open model. Drug elimination is restricted to the central compartment.

of the input and disposition functions (2.1) and (2.2), respectively. Therefore,

$$a_{s,c} = X_0 \frac{\prod_{i=2}^{n} (s + E_i)}{\prod_{i=1}^{n} (s + \lambda_i)} \tag{2.3}$$

Equation (2.3) may be solved for X_c, the amount of drug in the central compartment, by taking the anti-Laplace of this equation employing the general method of partial fractions (see Appendix B).

$$X_c = X_0 \sum_{\ell=1}^{n} \frac{\prod_{\substack{i=2 \\ i\neq\ell}}^{n} (E_i - \lambda_\ell)}{\prod_{\substack{i=1 \\ i\neq\ell}}^{n} (\lambda_i - \lambda_\ell)} e^{-\lambda_\ell t} \tag{2.4}$$

Although the central compartment is obviously not homogeneous, by assuming that the ratio of drug concentrations in the various tissues and fluids of the central compartment is constant (i.e., there is very rapid distribution between the plasma and the fluids and tissues of the central compartment), a linear relationship exists between the drug concentration in the plasma C and the amount of drug in the central compartment. That is,

$$X_c = V_c C \tag{2.5}$$

where V_c is the apparent volume of the central compartment. This relationship enables the conversion of (2.4) from an amount-time to a concentration-time equation which can be expressed as

$$C = \frac{X_0}{V_c} \sum_{\ell=1}^{n} \frac{\prod_{\substack{i=2 \\ i\neq\ell}}^{n} (E_i - \lambda_\ell)}{\prod_{\substack{i=1 \\ i\neq\ell}}^{n} (\lambda_i - \lambda_\ell)} e^{-\lambda_\ell t} \tag{2.6}$$

or

$$C = \sum_{\ell=1}^{n} A_\ell e^{-\lambda_\ell t} \tag{2.7}$$

where

$$A_\ell = \frac{X_0}{V_c} \frac{\prod_{\substack{i=2 \\ i\neq\ell}}^{n} (E_i - \lambda_\ell)}{\prod_{\substack{i=1 \\ i\neq\ell}}^{n} (\lambda_i - \lambda_\ell)} \tag{2.8}$$

A plot of the logarithm of drug plasma concentration versus time according to (2.7) will yield a multiexponential curve (Fig. 2.4). The disposition constants λ_1 to λ_{n-1} are by definition larger than λ_n; therefore, at some time the terms $A_1e^{-\lambda_1 t}$ to $A_{n-1}e^{-\lambda_{n-1} t}$ will approach zero, whereas $A_ne^{-\lambda_n t}$ will still have a finite value. Equation (2.7) will then reduce to

$$C = A_n e^{-\lambda_n t} \tag{2.9}$$

which in common logarithms is

$$\log C = \log A_n - \frac{\lambda_n t}{2.303} \tag{2.10}$$

Hence an estimate of λ_n can be obtained from the slope, $-\lambda_n/2.303$, of the terminal exponential phase, and the biologic half life $t_{1/2}$ can be determined either directly from the terminal phase or by employing the following relationship:

$$t_{1/2} = \frac{0.693}{\lambda_n} \tag{2.11}$$

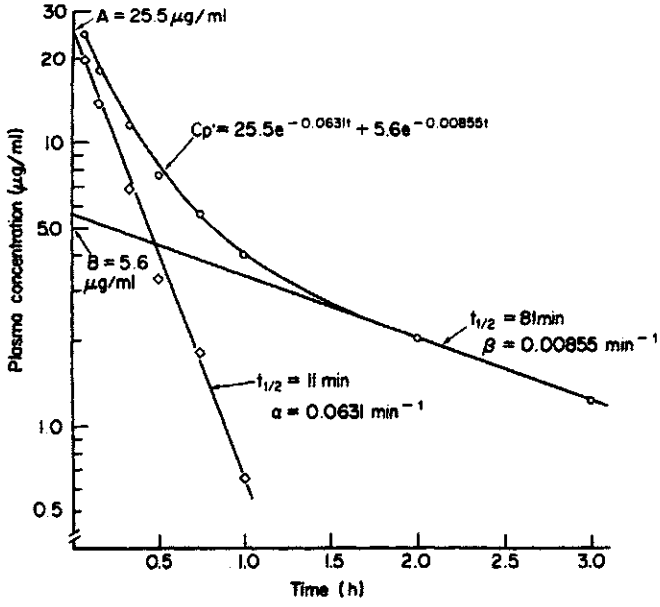


Fig. 2.4 Plasma levels of pralidoxime after intravenous administration of the iodine salt to a healthy volunteer. The data (O) are described by a biexponential equation; the method of residuals has been applied. In the notation of the text, A, B, α, β, and C_p correspond to A_1, A_2, λ_1, λ_2, and C, respectively. O Experimental values, ◇ residuals. (Data from Ref. 3, subject 2663, dose = 10 mg/kg.)

The zero-time intercept obtained by extrapolation of the terminal linear phase to t = 0 is A_n. Successive application of the method of residuals (Appendix C) will yield linear segment(s) with slope(s) and intercept(s) from which the remaining value(s) of λ and A can be determined.

The constants A_ℓ and λ_ℓ may be obtained graphically as shown in Fig. 2.4 or with the aid of a digital computer. The best approach is to fit the entire plasma concentration-time curve by means of a digital computer program which provides a nonlinear regression analysis of the curve (Appendix H). Once these experimental constants are obtained, other pharmacokinetic parameters can be readily generated.

At time t = 0, (2.7) becomes

$$C_0 = \sum_{\ell=1}^{n} A_\ell \tag{2.12}$$

where C_0 is the zero-time plasma concentration. Substituting the value of A_ℓ from (2.8) into (2.12) yields

$$C_o = \frac{X_0}{V_c} \sum_{\ell=1}^{n} \frac{\prod_{i=2}^{n} (E_i - \lambda_\ell)}{\prod_{\substack{i=1 \\ i \neq \ell}}^{n} (\lambda_i - \lambda_\ell)} \tag{2.13}$$

which simplifies to

$$C_0 = \frac{X_0}{V_c} \tag{2.14}$$

for any multicompartment model. Substitution of $\Sigma_{\ell=1}^{n} A_\ell$ for C_0, according to (2.12), into (2.14), and rearrangement yields the following expression, from which the apparent volume of the central compartment can be estimated:

$$V_c = \frac{X_0}{\sum_{\ell=1}^{n} A_\ell} \tag{2.15}$$

where X_0 is the intravenous dose.

Drug Levels in a Peripheral or "Tissue" Compartment

The differential equation describing the rate of change in the amount of drug in a peripheral compartment X_{pj} is

$$\frac{dX_{pj}}{dt} = k_{1j}X_c - E_jX_{pj} \tag{2.16}$$

where k_{1j} is the first-order intercompartmental transfer rate constant from the central to the peripheral compartment. The value of j varies from 2 to n. The Laplace transform of (2.16) (see Appendix B) is given by

$$s(a_{s,p}) = k_{1j}(a_{s,c}) - E_j(a_{s,p}) \tag{2.17}$$

Solving for $a_{s,p}$ and substituting the value of $a_{s,c}$ as given in (2.3) yields

$$a_{s,p} = X_0 \frac{k_{1j}}{s + E_j} \frac{\prod_{i=2}^{n} (s + E_i)}{\prod_{i=1}^{n} (s + \lambda_i)} \tag{2.18}$$

the anti-Laplace of which is (see Appendix B)

$$X_{pj} = X_0 \sum_{\ell=1}^{n} \frac{k_{1j}}{E_j - \lambda_\ell} \frac{\prod_{i=2}^{n} (E_i - \lambda_\ell)}{\prod_{\substack{i=1 \\ i \neq \ell}}^{n} (\lambda_i - \lambda_\ell)} e^{-\lambda_\ell t} \tag{2.19}$$

This equation describes the time course of the amount of drug in the peripheral compartment following intravenous administration. It is obvious from (2.19) that after a sufficiently long period of time the exponential terms $e^{-\lambda_1 t}$ to $e^{-\lambda_{n-1} t}$ will approach zero and (2.19) reduces to

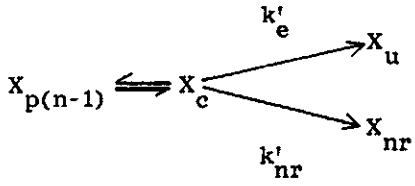
$$X_{pj} = X_0 \frac{k_{1j}}{E_j - \lambda_n} \frac{\prod_{i=2}^{n} (E_i - \lambda_n)}{\prod_{\substack{i=1 \\ i \neq \ell}}^{n} (\lambda_i - \lambda_n)} e^{-\lambda_n t} \tag{2.20}$$

Hence the slope of the terminal exponential phase of a semilogarithmic plot of tissue level versus time equals $-\lambda_n/2.303$. Therefore, in the postdistributive phase, plasma and peripheral compartment levels decline in parallel. This is illustrated in Fig. 2.5.

Urinary Excretion Data

It may be possible to obtain from urinary excretion data the pharmacokinetic parameters of a drug that confers on the body the pharmacokinetic characteristics of a multicompartment model. For a drug eliminated from the body partly by nonrenal processes a scheme analogous to Scheme 1 of Chap. 1 can be drawn:

Scheme 1



where X_u and X_{nr} are the respective cumulative amounts of unchanged drug eliminated in the urine and drug eliminated by all nonrenal path-

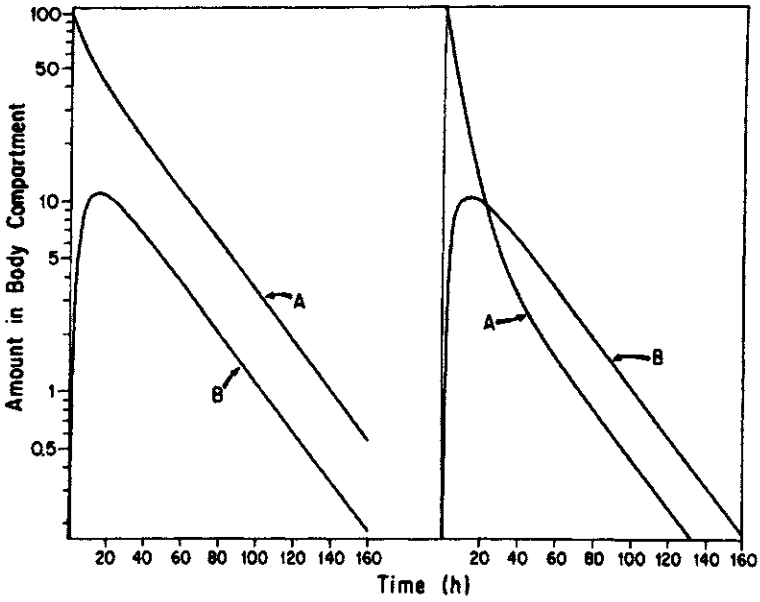


Fig. 2.5 Semilogarithmic plots of the amounts of drug in the central (A) and peripheral (B) compartments following intravenous administration of two drugs, each of which confer the pharmacokinetic characteristics of a two-compartment open model on the body, but which have different distribution characteristics.

ways to time t. The elimination rate constant from the central compartment, k_{10}, is the sum of the individual rate constants that characterize the parallel elimination processes. Therefore, $k_{10} = k'_e + k'_{nr}$, where k'_e is the apparent first-order rate constant for renal excretion and k'_{nr} is the sum of all other apparent first-order elimination rate constants for drug elimination by nonrenal pathways.

The excretion rate of intact drug, dX_u/dt, can be defined as

$$\frac{dX_u}{dt} = k'_e X_c \tag{2.21}$$

where X_c is as defined previously. Substitution for X_c, according to (2.4), into (2.21) yields

$$\frac{dX_u}{dt} = k'_e X_0 \sum_{\ell=1}^{n} \frac{\prod_{i=2}^{n} (E_i - \lambda_\ell)}{\prod_{\substack{i=1 \\ i\neq\ell}}^{n} (\lambda_i - \lambda_\ell)} e^{-\lambda_\ell t} \tag{2.22}$$

or

$$\frac{dX_u}{dt} = \sum_{\ell=1}^{n} A'_\ell e^{-\lambda_\ell t} \tag{2.23}$$

where

$$A'_\ell = k'_e X_0 \frac{\prod_{i=2}^{n} (E_i - \lambda_\ell)}{\prod_{\substack{i=1 \\ i\neq\ell}}^{n} (\lambda_i - \lambda_\ell)} \tag{2.24}$$

A semilogarithmic plot of excretion rate of unmetabolized drug versus time according to (2.23) will yield a multiexponential curve (Fig. 2.6). As with the semilogarithmic plasma concentration-time plot, λ_n can be obtained from the slope, $-\lambda_n/2.303$, of the terminal exponential phase, and the biologic half-life $t_{1/2}$ can be determined either directly from the terminal phase or from λ_n by (2.11). A'_n can be obtained by extrapolation of the terminal linear phase to time zero. Application of the method of residuals (Appendix C) permits estimates of the remaining value(s) of λ and A'. As with plasma concentration-time data, the constants λ_ℓ and A'_ℓ can be better obtained with the aid of a digital computer (Appendix H). It must be emphasized that the terminal slope of the log excretion rate versus time curve is a function of the overall elimination rate constant λ_n and not of the urinary excretion rate constant k'_e. However, k'_e can be calculated once the experimental constants λ_ℓ and A'_ℓ are obtained. The sum of the zero-time intercepts is given by

$$\sum_{\ell=1}^{n} A'_\ell = k'_e X_0 \sum_{\ell=1}^{n} \frac{\prod_{i=2}^{n} (E_i - \lambda_\ell)}{\prod_{\substack{i=1 \\ i\neq\ell}}^{n} (\lambda_i - \lambda_\ell)} \tag{2.25}$$

This equation can be simplified to

$$\sum_{\ell=1}^{n} A'_\ell = k'_e X_0 \tag{2.26}$$

which when rearranged yields the following expression for k'_e:

$$k'_e = \frac{\sum_{\ell=1}^{n} A'_\ell}{X_0} \tag{2.27}$$

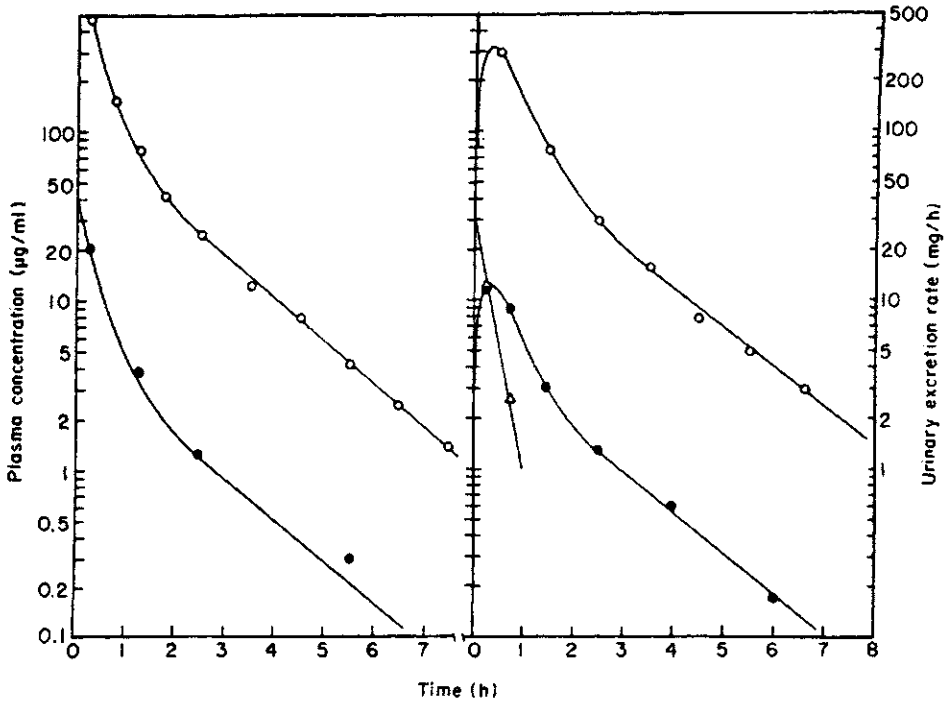


Fig. 2.6 Plasma concentrations (○) and urinary excretion rates (●) of ampicillin (left) after intravenous injection of ampicillin itself or of its prodrug, hetacillin (right). The triangles (right) indicate hetacillin concentrations in plasma. (Data from Ref. 4.)

Therefore, by knowing the intravenous dose and the values of A'_ℓ, the urinary excretion rate constant of intact drug can be determined.

An alternative approach, the sigma-minus method, is also available, from which the parameters of a multicompartment model can be evaluated based on urinary excretion data. The Laplace transform of (2.21) for the amount of drug in the urine $a_{s,u}$ is

$$s(a_{s,u}) = k'_e(a_{s,c}) \tag{2.28}$$

Substitution for $a_{s,c}$ from (2.3) and rearrangement yields

$$a_{s,u} = k'_e X_0 \frac{\prod_{i=2}^{n} (s + E_i)}{\prod_{i=1}^{n} s(s + \lambda_i)} \tag{2.29}$$

Solving (2.29) (see Appendix B) produces the following relationship between the amount of drug in the urine and time:

$$X_u = k'_e X_0 \frac{\prod_{i=2}^{n} E_i}{\prod_{i=1}^{n} \lambda_i} + k'_e X_0 \sum_{\ell=1}^{n} \frac{\prod_{i=2}^{n} (E_i - \lambda_\ell)}{\prod_{\substack{i=1 \\ i\neq\ell}}^{n} -\lambda_\ell(\lambda_i - \lambda_\ell)} e^{-\lambda_\ell t} \tag{2.30}$$

where X_u is the cumulative amount of unchanged drug excreted in the urine to time t. The amount of unmetabolized drug ultimately eliminated in the urine, X_u^∞, can be determined by setting time in (2.30) equal to infinity:

$$X_u^\infty = k'_e X_0 \frac{\prod_{i=2}^{n} E_i}{\prod_{i=1}^{n} \lambda_i} \tag{2.31}$$

Substitution of X_u^∞ for $k'_e X_0 \prod_{i=2}^{n} E_i / \prod_{i=1}^{n} \lambda_i$ in (2.30) and rearrangement yields

$$X_u^\infty - X_u = k'_e X_0 \sum_{\ell=1}^{n} \frac{\prod_{i=2}^{n} (E_i - \lambda_\ell)}{\prod_{\substack{i=1 \\ i\neq\ell}}^{n} \lambda_\ell(\lambda_i - \lambda_\ell)} e^{-\lambda_\ell t} \tag{2.32}$$

or

$$X_u^\infty - X_u = \sum_{i=\ell}^{n} A''_\ell e^{-\lambda_\ell t} \tag{2.33}$$

where

$$A''_\ell = k'_e X_0 \frac{\prod_{i=2}^{n} (E_i - \lambda_\ell)}{\prod_{\substack{i=1 \\ i\neq\ell}}^{n} \lambda_\ell(\lambda_i - \lambda_\ell)} \tag{2.34}$$

A plot of the logarithm of the amount of unchanged drug remaining to be excreted versus time is multiexponential (Fig. 2.7), and the slope

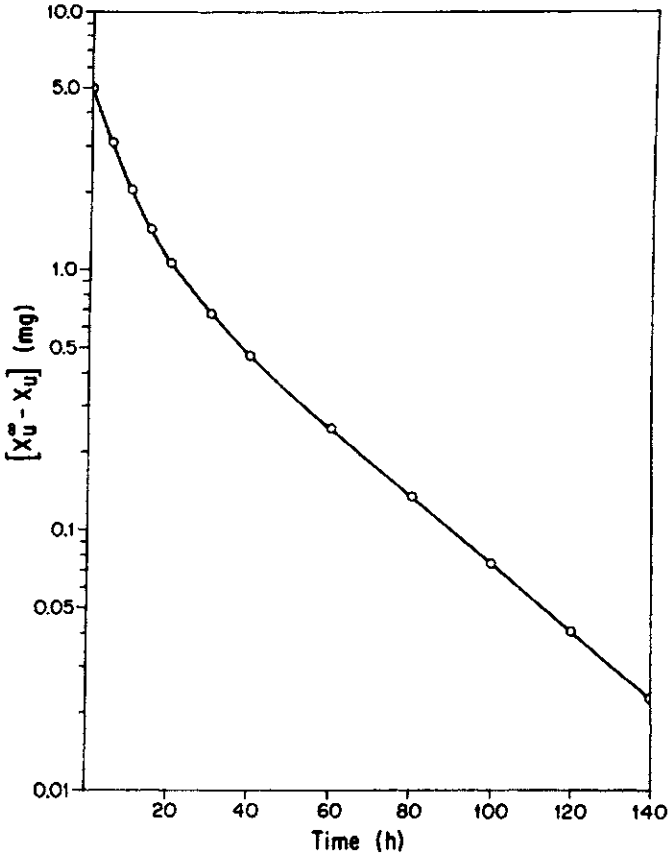


Fig. 2.7 Semilogarithmic plot of the amount of drug remaining to be excreted following intravenous administration of a drug. The data are described by Eq. (2.33), where n = 2.

of the terminal exponential phase is $-\lambda_n/2.303$, the same slope as a plot of log C versus t or a plot of log (dX_u/dt) versus t. The zero-time intercept of the extrapolated terminal linear phase yields A_n''. The other values of λ_ℓ and A_ℓ'' can be obtained from the slope(s) and intercept(s), respectively, of the residual line(s).

The general merits of these two urinary excretion methods, the excretion rate method and sigma-minus method, have been discussed in Chap. 1. It is important to emphasize that the value of urinary excretion data to obtain the pharmacokinetic parameters of a multicompartment model may be limited. In order to perform a multicompartment analysis of urinary excretion data, urine must be collected

with sufficient frequency to enable the characterization of the distributive phase. Since it is difficult to collect urine samples at a frequency of greater than every half-hour, the drug being examined must have a significant distributive phase. This problem is usually not encountered with plasma-level data because plasma samples can generally be collected with almost any desired frequency.

Renal Clearance

One can characterize the kinetics of renal excretion of a drug by a clearance value as well as by an excretion rate constant. The concept of clearance is discussed in Chap. 8. Renal clearance, as defined in Chap. 1, is the volume of blood flowing through the kidney per unit time from which all drug is extracted and excreted. In pharmacokinetic terms, renal clearance Cl_r is the urinary excretion rate divided by the blood or plasma concentration of drug at the midpoint of the urine collection period:

$$Cl_r = \frac{dX_u/dt}{C} \tag{2.35}$$

Replacement of dX_u/dt by $k'_e X_c$, according to (2.21), yields

$$Cl_r = \frac{k'_e X_c}{C} \tag{2.36}$$

Recognizing that X_c/C equals V_c [Eq. (2.5)], the following expression for renal clearance can be obtained:

$$Cl_r = k'_e V_c \tag{2.37}$$

Therefore, renal clearance equals the product of the renal excretion rate constant k'_e and the apparent volume of the central compartment V_c. If renal clearance is determined independently by (2.35) and if an estimate of V_c is available, (2.37) may be employed to calculate k'_e. This method for determining k'_e has an advantage over the method which employs (2.27) in that estimates of the zero-time intercepts of an excretion rate plot, A'_2, may be difficult to obtain.

Probably a more satisfactory method for determining clearance than the one-point determination obtained by employing (2.35) would be to rearrange Eq. (2.35) (i.e., $dX_u/dt = Cl_r C$) and to plot excretion rate versus the plasma concentration at the midpoint of each urine collection period. The slope of such a plot equals renal clearance. The utilization of rate plots is discussed in Appendix F.

Recognizing that renal clearance as defined by (2.35) equals $k_e V$ for a one-compartment model [Eq. (1.25)] and $k'_e V_c$ for a multicompartment model, it can be readily shown that (1.27) and (1.28) also apply to multicompartment models:

$$(X_u)_{t_1}^{t_2} = Cl_r \int_{t_1}^{t_2} C\ dt \tag{2.38}$$

and

$$Cl_r = \frac{X_u^{\infty}}{\int_0^{\infty} C\ dt} = \frac{X_u^{\infty}}{AUC} \tag{2.39}$$

respectively. The term $(X_u)_{t_1}^{t_2}$ is the amount of unmetabolized drug eliminated in the urine during the time interval t_1 to t_2, and $\int_{t_1}^{t_2} C\ dt$ is the area under the blood or plasma concentration versus time curve during the same time interval t_1 to t_2. $\int_0^{\infty} C\ dt$ or AUC represents the total area under the drug concentration in the blood or plasma-time curve. Therefore, by employing (2.38), an estimate of the renal clearance of a drug, which distributes in the body according to a multicompartment model, may be obtained from the slope of a plot of the amounts of unmetabolized drug eliminated in the urine during time intervals t_1 to t_2 $[(X_u)_{t_1}^{t_2}]$ versus the areas under the plasma concentration-time curve (plotted on rectilinear graph paper) during the same time intervals ($\int_{t_1}^{t_2} C\ dt$). The average renal clearance of a drug can be determined using (2.39) if the total amount of unmetabolized drug eliminated in the urine and the area under the plasma concentration-time curve from time zero to infinity are known.

The total area under the curve as required by (2.39) for the calculation of renal clearance can be readily determined employing the relationship

$$AUC = \sum_{\ell=1}^{n} \frac{A_\ell}{\lambda_\ell} \tag{2.40}$$

which results from the integration of (2.7) from time zero to infinity.

Systemic Clearance

Systemic clearance Cl_s or total body clearance is the sum of clearances for all processes involved in the elimination of a drug from the body and can be given by an expression analogous to (2.35), the equation for renal clearance:

$$Cl_s = \frac{dX_E/dt}{C} \tag{2.41}$$

where dX_E/dt is the rate of drug elimination by all routes of elimination. Solving (2.41) for dX_E/dt and integrating the resulting expression from time zero to infinity yields

$$(X_E)_0^\infty = Cl_s \int_0^\infty C\,dt = Cl_s \cdot AUC \tag{2.42}$$

where $(X_E)_0^\infty$ is the total amount of drug eliminated, which must be equal to the dose X_0 of drug administered when the drug is given intravenously. Therefore, substitution of X_0 for $(X_E)_0^\infty$ in (2.42) and rearrangement provides the following expression for clearance:

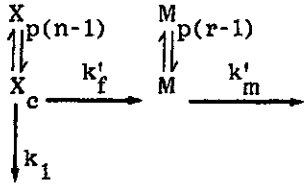
$$Cl_s = \frac{X_0}{AUC} \tag{2.43}$$

Clearance is extensively discussed in Chap. 8.

Metabolite Levels in the Plasma

The formation of a metabolite that distributes in the body according to a multicompartment model following the intravenous administration of a drug which also distributes according to a multicompartment model is illustrated in Scheme 2:

Scheme 2



X_p and X_c are as defined previously; M and M_p are the amounts of metabolite in the central and peripheral body compartments, respectively; the constants k'_f and k'_m are the apparent first-order formation and elimination rate constants, respectively, of the metabolite; and k_1 is the sum of all apparent first-order elimination rate constants for all processes other than metabolism. In this scheme $k_{10} = k_1 + k'_f$, where k_{10} is the elimination rate constant from the central compartment for parent drug.

The disposition functions for the drug, $d_{s,c}$, and metabolite, $d_{s,m}$, in their respective central compartments (see Appendix B) are

$$d_{s,c} = \frac{\prod_{i=2}^{n} (s + E_i)}{\prod_{i=1}^{n} (s + \lambda_i)}$$

[Eq. (2.1)] and

$$d_{s,m} = \frac{\prod_{j=2}^{r} (s + E_j)}{\prod_{j=1}^{r} (s + \gamma_j)} \tag{2.44}$$

respectively, where E_i and λ_i are as defined previously, E_j is the sum of the exit rate constants from the jth compartment for the metabolite, and γ_j is a disposition rate constant associated with the blood or plasma concentration-time curve following an intravenous bolus injection of metabolite and is analogous to λ_i. The Laplace transform for the amount of drug in the central compartment, $a_{s,c}$, following intravenous injection is given by

$$a_{s,c} = X_0 \frac{\prod_{i=2}^{n} (s + E_i)}{\prod_{i=1}^{n} (s + \lambda_i)}$$

[Eq. (2.3)]. The input function into the central compartment for the metabolite, $in_{s,m}$, is given by

$$in_{s,m} = k_f'(a_{s,c}) \tag{2.45}$$

Therefore, the Laplace transform for the amount of metabolite in the central compartment, $a_{s,m}$, following the intravenous injection of a drug is given by the product of (2.44) and (2.45):

$$a_{s,m} = k_f'(a_{s,c}) \frac{\prod_{j=2}^{r} (s + E_j)}{\prod_{j=1}^{r} (s + \gamma_j)} \tag{2.46}$$

Substitution for $a_{s,c}$, according to (2.3), in (2.46) yields

$$a_{s,m} = k_f' X_0 \frac{\prod_{i=2}^{n} (s + E_i)}{\prod_{i=1}^{n} (s + \lambda_i)} \frac{\prod_{j=2}^{r} (s + E_j)}{\prod_{j=1}^{r} (s + \gamma_j)} \tag{2.47}$$

Taking the anti-Laplace of (2.47) and writing a general equation for the concentration of metabolite in the plasma, C_m, gives

$$C_m = \sum_{\ell=1}^{n} A_\ell e^{-\lambda_\ell t} + \sum_{u=1}^{r} B_u e^{-\gamma_u t} \qquad (2.48)$$

Equation (2.48) indicates that a minimum of five exponential terms are required to describe the time course of a relatively slowly distributing metabolite which is formed after intravenous administration of a drug with multicompartment characteristics. In fact, metabolite concentration-time curves rarely require more than two or three exponential terms to describe them, reflecting a lack of discrimination of individual rate processes. A rigorous analysis of metabolite concentration-time data will provide little information concerning the multicompartment pharmacokinetics of the parent drug or even concerning the metabolite itself. The slope of the terminal linear segment of a semilogarithmic plot of metabolite concentration versus time will probably be equal to either $-\lambda_n/2.303$ or $-\gamma_r/2.303$, whichever is smaller. Residual analysis will almost always result in hybrid constants that cannot be related to either the drug or the metabolite.

INTRAVENOUS INFUSION

Drug Concentrations in the Plasma

The disposition function for the central compartment following constant rate intravenous infusion of a drug that confers the pharmacokinetic characteristics of a multicompartment model on the body is identical to the disposition function for an intravenous bolus injection [Eq. (2.1)]:

$$d_{s,c} = \frac{\prod_{i=2}^{n} (s + E_i)}{\prod_{i=1}^{n} (s + \lambda_i)}$$

where all parameters are as defined previously. For intravenous infusion the input function in_s is given by

$$in_s = \frac{k_0(1 - e^{-Ts})}{s} \qquad (2.49)$$

where k_0 is the zero-order infusion rate in units of amount per time and T is the time when infusion ends. The Laplace transform for the amount of drug in the central compartment, $a_{s,c}$ is given by the product of the input and disposition function, (2.49) and (2.1), respectively. Hence

$$a_{s,c} = \frac{k_0(1 - e^{-Ts})}{s} \frac{\prod_{i=2}^{n} (s + E_i)}{\prod_{i=1}^{n} (s + \lambda_i)} \tag{2.50}$$

One may solve for X_c, the amount of drug in the central compartment, by taking the anti-Laplace of (2.50) (see Appendix B). The resulting equation is

$$X_c = k_0 \sum_{\ell=1}^{n} \frac{(1 - e^{\lambda_\ell T}) \prod_{i=2}^{n} (E_i - \lambda_\ell)}{-\lambda_\ell \prod_{\substack{i=1 \\ i \neq \ell}}^{n} (\lambda_i - \lambda_\ell)} e^{-\lambda_\ell t} \tag{2.51}$$

which can be written in concentration terms, employing the relationship $X_c = V_c C$ according to (2.5), as follows:

$$C = \frac{k_0}{V_c} \sum_{\ell=1}^{n} \frac{(1 - e^{\lambda_\ell T}) \prod_{i=2}^{n} (E_i - \lambda_\ell)}{-\lambda_\ell \prod_{\substack{i=1 \\ i \neq \ell}}^{n} (\lambda_i - \lambda_\ell)} e^{-\lambda_\ell t} \tag{2.52}$$

This equation describes the time course of drug in the plasma during infusion and after cessation of infusion. While infusion is continuing, $T = t$ and varies with time. When infusion ceases, T becomes a constant corresponding to the time infusion was stopped. Hence, by utilization of (2.52), the total plasma concentration-time curve during and following infusion can be fit with the aid of a digital computer. Consequently, it is not necessary to fit infusion curves by two discrete equations, one representing the infusion period and one representing the postinfusion period [5].

During infusion, $T = t$, and the term $(1 - e^{\lambda_\ell T})e^{-\lambda_\ell t}$ in (2.52) becomes $(e^{-\lambda_\ell t} - 1)$. Therefore,

$$C = \frac{k_0}{V_c} \sum_{\ell=1}^{n} \frac{\prod_{i=2}^{n} (E_i - \lambda_\ell)}{-\lambda_\ell \prod_{\substack{i=1 \\ i \neq \ell}}^{n} (\lambda_i - \lambda_\ell)} (e^{-\lambda_\ell t} - 1) \tag{2.53}$$

Expansion yields

$$C = \frac{k_0}{V_c}\left[\sum_{\ell=1}^{n} \frac{\prod_{\substack{i=2 \\ i\neq\ell}}^{n}(E_i - \lambda_\ell)}{\lambda_\ell \prod_{\substack{i=1 \\ i\neq\ell}}^{n}(\lambda_i - \lambda_\ell)} - \sum_{\ell=1}^{n} \frac{\prod_{\substack{i=2 \\ i\neq\ell}}^{n}(E_i - \lambda_\ell)}{\lambda_\ell \prod_{\substack{i=1 \\ i\neq\ell}}^{n}(\lambda_i - \lambda_\ell)} e^{-\lambda_\ell t}\right] \tag{2.54}$$

The first term in (2.54) can be simplified to give the following equation for C:

$$C = \frac{k_0}{V_c}\left[\frac{\prod_{i=2}^{n} E_i}{\prod_{i=1}^{n} \lambda_i} - \sum_{\ell=1}^{n} \frac{\prod_{\substack{i=2 \\ i\neq\ell}}^{n}(E_i - \lambda_\ell)}{\lambda_\ell \prod_{\substack{i=1 \\ i\neq\ell}}^{n}(\lambda_i - \lambda_\ell)} e^{-\lambda_\ell t}\right] \tag{2.55}$$

This equation describes the rise in drug concentration with time after the start of intravenous infusion. Plasma concentrations will increase with time until the rate of elimination equals the rate of infusion and then will remain constant. This plateau plasma drug concentration C_{ss} can be determined from (2.55) by setting time equal to infinity (i.e., by recognizing that the term $e^{-\lambda_\ell t}$ approaches zero with time). Thus

$$C_{ss} = \frac{k_0 \prod_{i=2}^{n} E_i}{V_c \prod_{i=1}^{n} \lambda_i} \tag{2.56}$$

It is evident that the plateau or steady-state concentration C_{ss} of drug is directly proportional to the rate of infusion. The term $\prod_{i=2}^{n} E_i / V_c \prod_{i=1}^{n} \lambda_i$ can be expanded to $k_{21}k_{31}\cdots k_{n1}/V_c\lambda_1\lambda_2\lambda_3\cdots\lambda_n$, which is equal to $1/V_c k_{10}$ or $1/Cl_s$ [see Eqs. (2.107), 2.169), and (2.215)]. Therefore, substitution of $1/Cl_s$ into (2.56) yields

$$C_{ss} = \frac{k_0}{Cl_s} \tag{2.57}$$

By knowing the clearance of a drug, the infusion rate required to maintain a certain plasma concentration of drug can be readily calculated employing the following rearrangement of (2.57):

$$k_0 = C_{ss}Cl_s \tag{2.58}$$

As is apparent from (2.57), the systemic clearance of a drug is readily calculated from the ratio of infusion rate to steady-state drug concentration in plasma:

$$Cl_s = \frac{k_0}{C_{ss}} \tag{2.59}$$

The terminal disposition rate constant, and hence half-life, of a drug may also be determined from data collected during infusion to steady state. Expansion of (2.55), substitution of C_{ss} for $k_0 \prod_{i=2}^{n} E_i / V_c \prod_{i=1}^{n} \lambda_i$ according to (2.56), and rearrangement gives

$$C_{ss} - C = \frac{k_0}{V_c} \sum_{\ell=1}^{n} \frac{\prod_{i=2}^{n} (E_i - \lambda_\ell)}{\lambda_\ell \prod_{\substack{i=1 \\ i\neq\ell}}^{n} (\lambda_i - \lambda_\ell)} e^{-\lambda_\ell t} \tag{2.60}$$

Based on this relationship, a plot of log $(C_{ss} - C)$ versus time will be nonlinear. However, since the values of λ_1 to λ_{n-1} are larger than λ_n, at some time during the infusion the terms $e^{-\lambda_1 t}$ to $e^{-\lambda_{n-1} t}$ will approach zero. At this time (2.60) will simplify to

$$C_{ss} - C = \frac{k_0 \prod_{i=2}^{n} (E_i - \lambda_n)}{V_c \lambda_n \prod_{\substack{i=1 \\ i\neq n}}^{n} (\lambda_i - \lambda_n)} e^{-\lambda_n t} \tag{2.61}$$

which in logarithmic terms becomes

$$\log (C_{ss} - C) = \log \frac{k_0 \prod_{i=2}^{n} (E_i - \lambda_n)}{V_c \lambda_n \prod_{\substack{i=1 \\ i\neq n}}^{n} (\lambda_i - \lambda_n)} - \frac{\lambda_n t}{2.303} \tag{2.62}$$

Therefore, a plot of log $(C_{ss} - C)$ versus t should eventually yield a linear segment with a slope of $-\lambda_n/2.303$ from which λ_n can be determined. Half-life $t_{1/2}$ can be determined either directly from the terminal linear segment of the resulting plot or from the relationship [Eq. (2.11)]

$$t_{1/2} = \frac{0.693}{\lambda_n}$$

The half-life and terminal disposition rate constant may also be determined from the declining drug concentration in the plasma versus time data collected following cessation of an intravenous infusion. Once infusion is stopped, T becomes a constant (i.e., the time at which infusion is ended). The term $(1 - e^{\lambda_\ell T})e^{-\lambda_\ell t}$ in (2.52) becomes $(1 - e^{\lambda_\ell T})e^{-\lambda_\ell (t'+T)}$ since

$$t = t' + T \tag{2.63}$$

where t' is the postinfusion time. Rearrangement of the term $(1 - e^{\lambda_\ell T})e^{-\lambda_\ell (t'+T)}$ yields $(e^{-\lambda_\ell T} - 1)e^{-\lambda_\ell t'}$. Therefore,

$$(1 - e^{\lambda_\ell T})e^{-\lambda_\ell t} = (e^{-\lambda_\ell T} - 1)e^{-\lambda_\ell t'} \tag{2.64}$$

in the postinfusion phase. Substitution of $(e^{-\lambda_\ell T} - 1)e^{-\lambda_\ell t'}$ for $(1 - e^{\lambda_\ell T})e^{-\lambda_\ell t}$ in (2.52) yields the following relationship between plasma concentration and time (t', postinfusion time) during the period after infusion [6]:

$$C = \frac{k_0}{V_c} \sum_{\ell=1}^{n} \frac{(e^{-\lambda_\ell T} - 1) \prod_{i=2}^{n} (E_i - \lambda_\ell)}{-\lambda_\ell \prod_{\substack{i=1 \\ i\neq\ell}}^{n} (\lambda_i - \lambda_\ell)} e^{-\lambda_\ell t'} \tag{2.65}$$

or

$$C = \sum_{\ell=1}^{n} R_\ell e^{-\lambda_\ell t'} \tag{2.66}$$

where

$$R_\ell = \frac{k_0}{V_c} \frac{(e^{-\lambda_\ell T} - 1) \prod_{i=2}^{n} (E_i - \lambda_\ell)}{-\lambda_\ell \prod_{\substack{i=1 \\ i\neq\ell}}^{n} (\lambda_i - \lambda_\ell)} \tag{2.67}$$

The coefficient R_ℓ can be related to A_ℓ, the zero-time intercept following intravenous injection. Rearrangement of (2.8) yields

$$\frac{A_\ell}{X_0} = \frac{\prod_{i=2}^{n} (E_i - \lambda_\ell)}{V_c \prod_{\substack{i=1 \\ i \neq \ell}}^{n} (\lambda_i - \lambda_\ell)} \tag{2.68}$$

Substituting A_ℓ/X_0 for $\prod_{i=2}^{n} (E_i - \lambda_\ell)/[V_c \prod_{i=1, i\neq\ell}^{n} (\lambda_i - \lambda_\ell)]$ in (2.67) and solving for A_ℓ gives the relationship

$$A_\ell = \frac{R_\ell X_0 \lambda_\ell}{k_0(1 - e^{-\lambda_\ell T})} \tag{2.69}$$

where X_0 is the administered dose and equals the product of the infusion rate and the infusion time (i.e., k_0T).

From (2.66) it is readily apparent that upon stopping the infusion, drug concentrations in the plasma decline in a multiexponential manner when plotted semilogarithmically (Fig. 2.8). Determination of the constants λ_1 to λ_n and R_1 to R_n from postinfusion data may be carried out in the usual fashion (i.e., method of residuals, Appendix C, or computer curve-fitting, Appendix H). By knowing the duration of infusion and the infusion rate, A_1 to A_n can be calculated employing (2.69).

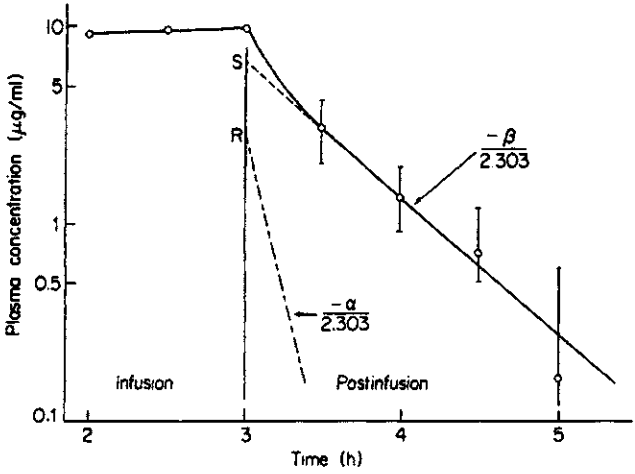


Fig. 2.8 Average oxacillin concentrations in plasma during and after constant rate intravenous infusion in four healthy volunteers. In the notation of the text, R, S, α, and β correspond to R_1, R_2, λ_1, and λ_2, respectively. (Data from Ref. 7.)

Equation (2.66), which describes the time course of drug following the cessation of infusion, is very useful since it is frequently difficult or impossible to administer a drug by rapid intravenous injection because of limited solubility of the drug (requiring a large injection volume), or because of possible adverse pharmacologic effects. It may then become necessary to inject the drug slowly (i.e., as a short intravenous infusion).

If infusion is carried out until steady state is attained [i.e., the infusion time T is sufficiently long so that the term $e^{-\lambda_\ell T}$ in (2.65) approaches zero], the zero-time intercept R_ℓ, as defined by (2.67), becomes

$$R_\ell = \frac{k_0}{V_c} \frac{\prod_{i=2}^{n} (E_i - \lambda_\ell)}{\lambda_\ell \prod_{\substack{i=1 \\ i \neq \ell}}^{n} (\lambda_i - \lambda_\ell)} \tag{2.70}$$

Therefore, the decline of drug in the plasma after cessation of infusion to steady state is given by

$$C = \frac{k_0}{V_c} \sum_{\ell=1}^{n} \frac{\prod_{i=2}^{n} (E_i - \lambda_\ell)}{\lambda_\ell \prod_{\substack{i=1 \\ i \neq \ell}}^{n} (\lambda_i - \lambda_\ell)} e^{-\lambda_\ell t'} \tag{2.71}$$

Equation (2.69) then reduces to

$$A_\ell = \frac{R_\ell X_0 \lambda_\ell}{k_0} \tag{2.72}$$

where R_ℓ is as defined by (2.70). Once R_1 to R_n and λ_1 to λ_n are estimated from postinfusion plasma concentration-time data, A_ℓ can be calculated employing (2.72).

If a two-compartment system is considered (i.e., n = 2), the larger the ratio of the zero-time intercepts A_1/A_2 following intravenous injection, the more readily one can discern the multicompartment characteristics of a drug. As A_1 approaches zero, the ratio A_1/A_2 approaches zero and the plasma concentration-time curve becomes monoexponential (Fig. 2.9). On the other hand, if A_1 is exceedingly large relative to A_2, the plasma curve may again appear to reflect a one-compartment model since, in this case, the plasma levels during the distributive phase may decline in an apparent mono-

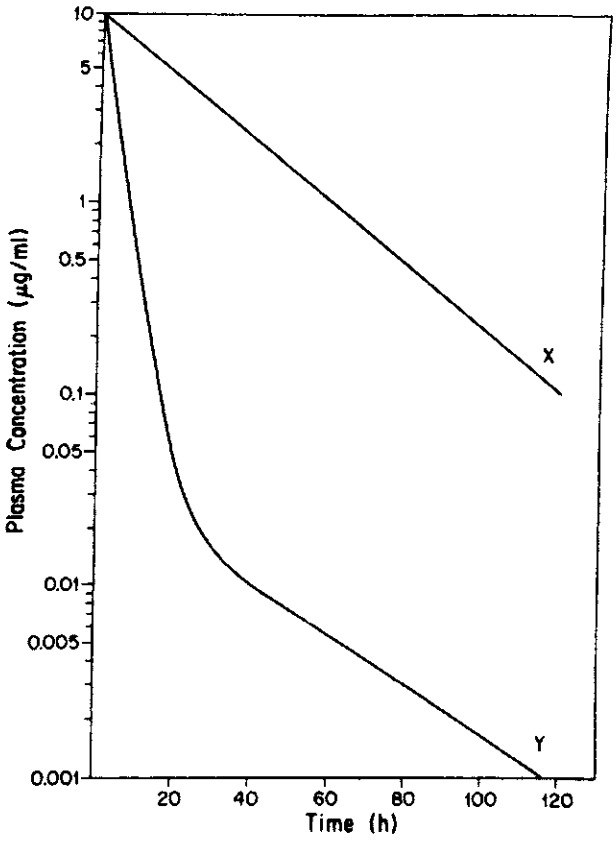


Fig. 2.9 Semilogarithmic plots of drug concentrations in plasma following intravenous injection of compounds X and Y. The disposition rate constants λ_1 and λ_2 are the same for both drugs, but the ratios of the coefficients (i.e., A_1/A_2) are markedly different, 0.3 for X and 300 for Y.

exponential fashion over several orders of magnitude of plasma drug concentration prior to reaching the terminal exponential phase (Fig. 2.9). This latter phase may not be observed, as the plasma concentration of drug may be well below the assay sensitivity for the drug in plasma.

For a drug that is administered by a bolus intravenous injection, the ratio of A_1 to A_2 is given by

$$\frac{A_1}{A_2} = \frac{\lambda_1 - E_2}{E_2 - \lambda_2} \tag{2.73}$$

where A_1 and A_2 are obtained from (2.8). However, when a drug is infused to steady state, the analogous ratio R_1/R_2 is given by

$$\frac{R_1}{R_2} = \frac{\lambda_1 - E_2}{E_2 - \lambda_2}\frac{\lambda_2}{\lambda_1} \tag{2.74}$$

where R_1 and R_2 are obtained from (2.70). It follows that the ratio R_1/R_2 will always be less than the ratio A_1/A_2 since λ_2 is by definition smaller than λ_1. As a result, the ability to discern the multicompartment characteristics of a drug following infusion is

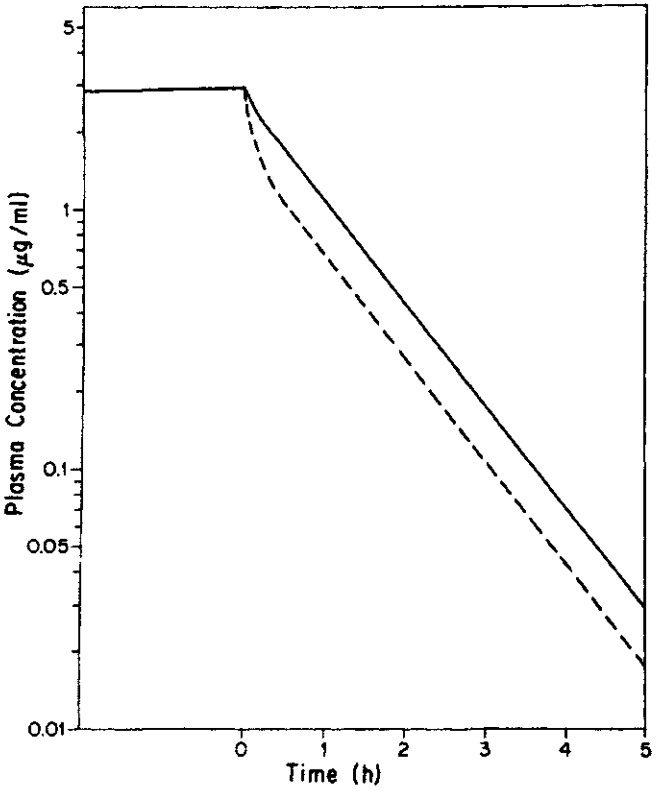


Fig. 2.10 Decline in plasma levels of a drug that confers two-compartment model characteristics on the body, following constant rate intravenous infusion to steady state (——) and following the rapid intravenous injection of a dose that gives an initial drug concentration equal to the steady-state concentration (- - - - -). The biexponential characteristic of the drug is more evident following the bolus injection than after terminating the infusion.

usually decreased (Fig. 2.10). Hence the determination of the multicompartment model parameters following intravenous infusion may be very difficult for drugs that do not display prominent multicompartment characteristics upon rapid intravenous injection. However, for drugs with a very high A_1/A_2 ratio, infusion may be advantageous from a pharmacokinetic analysis point of view since the multiexponential time course of a drug in the plasma may become more apparent. These general observations apply regardless of the number of compartments required to describe the disposition characteristics of a drug.

Simultaneous Rapid Intravenous Injection

The time required to obtain steady-state plasma levels C_{ss} by infusion will be quite long for a drug with a long half-life. It may be convenient in such cases to administer an intravenous loading dose to attain immediately the desired drug concentration and then attempt to maintain this concentration by continuous infusion. The equation describing the time course of the plasma concentration of drug following simultaneous injection of an intravenous loading dose and initiation of infusion is the sum of the two equations describing these two processes individually, Eqs. (2.6) and (2.55), respectively. Thus

$$C = \frac{X_0}{V_c} \sum_{\ell=1}^{n} \frac{\prod_{\substack{i=2 \\ i\neq\ell}}^{n} (E_i - \lambda_\ell)}{\prod_{\substack{i=1 \\ i\neq\ell}}^{n} (\lambda_i - \lambda_\ell)} e^{-\lambda_\ell t} + \frac{k_0}{V_c}\left[\frac{\prod_{i=2}^{n} E_i}{\prod_{i=1}^{n} \lambda_i} - \sum_{\ell=1}^{n} \frac{\prod_{\substack{i=2 \\ i\neq\ell}}^{n} (E_i - \lambda_\ell)}{\lambda_\ell \prod_{\substack{i=1 \\ i\neq\ell}}^{n} (\lambda_i - \lambda_\ell)} e^{-\lambda_\ell t}\right] \tag{2.75}$$

Expanding (2.75), collecting the coefficients of the exponential terms, and bringing these terms to a common denominator yields

$$C = \frac{k_0}{V_c} \frac{\prod_{i=2}^{n} E_i}{\prod_{i=1}^{n} \lambda_i} + \sum_{\ell=1}^{n} \frac{X_0\lambda_\ell - k_0}{V_c\lambda_\ell} \frac{\prod_{\substack{i=2 \\ i\neq\ell}}^{n} (E_i - \lambda_\ell)}{\prod_{\substack{i=1 \\ i\neq\ell}}^{n} (\lambda_i - \lambda_\ell)} e^{-\lambda_\ell t} \tag{2.76}$$

Since the variable, time, remains in (2.76), it is readily apparent that the plasma concentration following the intravenous injection and simultaneous intravenous infusion of a drug that distributes in the body according to a multicompartment model will not be constant. For the concentration of drug in plasma to be constant, the coefficient of the exponential term in (2.76) must equal zero. This will occur when either $X_0\lambda_i - k_0$ and/or $E_i - \lambda_i$ in (2.76) are zero. This situation is not possible unless n = 1 (i.e., a one-compartment model).

The loading dose required to give an immediate plasma concentration of drug equal to the steady-state level C_{ss} would be $C_{ss}V_c$, since V_c relates the amount of drug in the body at time zero (i.e., the dose) to the plasma concentration at time zero. However, when a loading dose of $C_{ss}V_c$ is administered, and infusion is simultaneously initiated at a rate equal to $C_{ss}Cl_s$ [Eq. (2.58)], the plasma level will fall below the desired steady-state concentration, reach a minimum, then gradually increase until C_{ss} is obtained (Fig. 2.11). An alternative approach is to administer a loading dose equal to $C_{ss}V_\beta$ with infusion at a rate equal to $C_{ss}Cl_s$. V_β is the apparent volume of distribution of a drug that relates plasma concentration to the amount of drug in the body during the terminal exponential phase

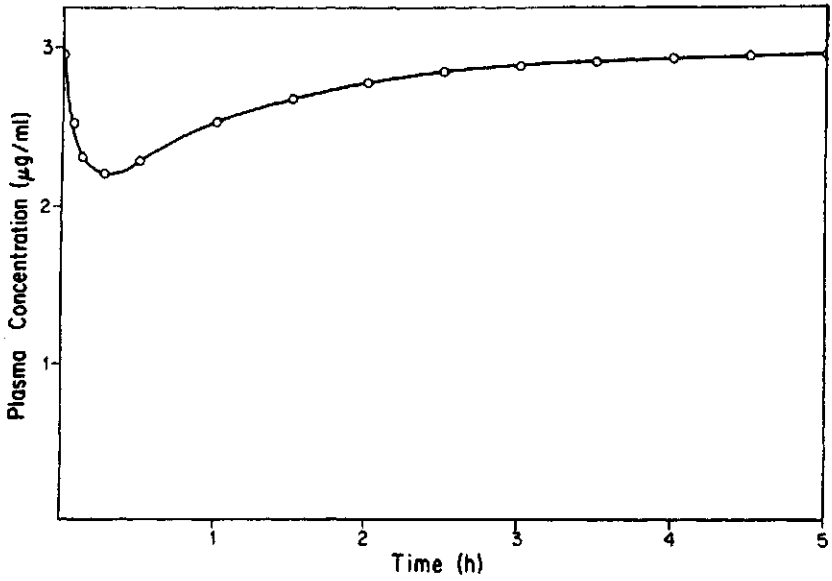


Fig. 2.11 Drug concentration in plasma on simultaneous rapid intravenous injection of a dose equal to $C_{ss}V_c$, and initiation and maintenance of an intravenous infusion at a rate equal to $C_{ss}Cl_s$. The drug in question displays multicomparment characteristics.

(i.e., $\ell = n$) of a plasma concentration versus time curve. This parameter is discussed in more detail later in the chapter. When a loading dose equal to $C_{ss}V_\beta$ is administered, the initial concentration of drug in the plasma will be higher than the desired steady-state level but will decrease with time to C_{ss} (Fig. 2.12). This alternative appears to be satisfactory for certain drugs (e.g., theophylline). However, with other drugs which also have a low therapeutic index (e.g., lidocaine), the initial levels may be sufficiently high as to produce toxicity. In practice a loading dose between the two extremes (i.e., between $V_C C_{ss}$ and $V_\beta C_{ss}$), although not ideal, would probably be the most satisfactory. This approach appears to have been successfully employed by Thomson et al. [9] and Rowland et al. [10] with lidocaine.

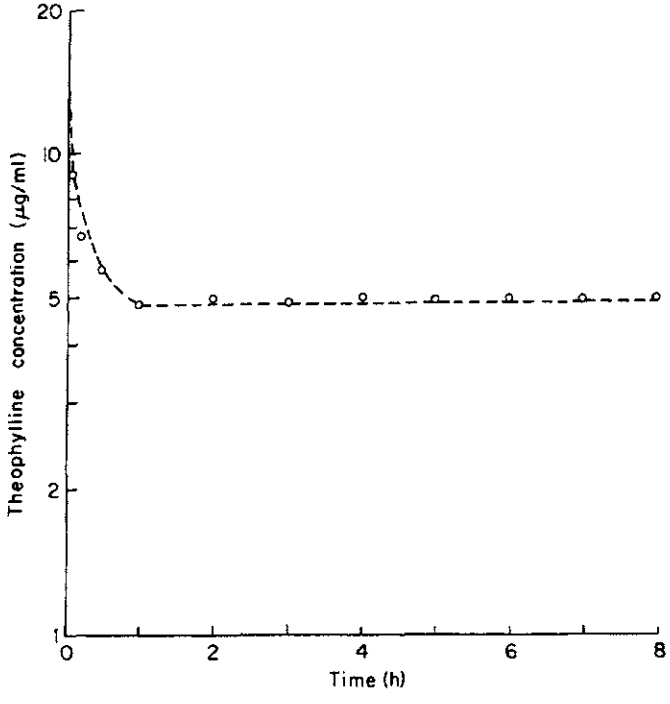


Fig. 2.12 Theophylline concentration in plasma on simultaneous rapid intravenous injection of a dose equal to $C_{ss}V_\beta$, and initiation and maintenance of an intravenous infusion at a rate equal to $C_{ss}Cl_s$. (From Ref. 8, subject F. S.; mean plateau concentration = 4.92 μg/ml).

Consecutive Constant Rate Intravenous Infusions

The administration of loading doses equal to $C_{ss}V_c$ or $C_{ss}V_\beta$, in conjunction with a zero-order infusion at a rate of $C_{ss}Cl_s$, presents disadvantages for drugs with pronounced multicompartment characteristics. The former may result in blood levels sufficiently below the desired drug concentration so that the patient is left unprotected for relatively long periods of time. The latter may produce untoward effects shortly after initiating therapy. An arbitrarily selected intermediate loading dose may still present one or the other problem. Interest in this issue has been considerable and several possible solutions have been considered.

Kruger-Thiemer [11] designed a dosing regimen for a drug with two-compartment characteristics that consists of an intravenous bolus dose equal to $C_{ss}V_c$ and a simultaneous intravenous infusion with an initial rate equal to $\lambda_1 C_{ss}V_c$ which decreases exponentially with time to a value of $C_{ss}Cl_s$. This approach is theoretically sound but presents formidable practical problems. Vaughan and Tucker [12], in an attempt to overcome the difficulties associated with administering a drug infusion at an exponentially declining rate, proposed approximating the exponential rate with a consecutive declining series of constant infusion rates.

A more realistic approach for the rapid achievement and maintenance of desired concentrations of drug in the plasma is the use of two consecutive constant rate intravenous infusions. The second or slower of the two infusions should be initiated immediately upon cessation of the first infusion, at a rate equal to $C_{ss}Cl_s$, where C_{ss} is equivalent to the desired drug concentration. Selection of the appropriate rate and appropriate infusion time for the first infusion is not as straightforward and requires consideration of several factors. Clearly, the initial infusion must be given at a sufficiently rapid rate to achieve desired drug concentrations shortly after initiating therapy. The first infusion must not be continued for too long a period; otherwise high blood levels associated with adverse effects may be reached. On the other hand, if the first infusion is discontinued too quickly, blood levels may fall below the desired range and remain there for an unacceptably long period of time.

The input function for the first infusion is given by Eq. (2.49):

$$in_{s1} = \frac{k_{01}(1 - e^{-Ts})}{s}$$

where k_{01} is the zero-order rate of the first infusion and T is the duration of this fast infusion. The input function for the second infusion, which is initiated at time T, is given by

$$in_{s2} = \frac{k_0(e^{-Ts} - e^{-T's})}{s} \tag{2.77}$$

where k_{02} is the zero-order rate of the second infusion and T' is the duration of this maintenance infusion. The disposition function $d_{s,c}$ for a multicompartment model has been described by Eq. (2.1).

The Laplace transform for the case where there are two consecutive infusions will be the sum of the two input functions in_{s1} and in_{s2} times the disposition function $d_{s,c}$. Therefore,

$$a_{s,c} = \left[\frac{k_{01}(1 - e^{-Ts})}{s} + \frac{k_{02}(e^{-Ts} - e^{-T's})}{s}\right] \frac{\prod_{i=2}^{n}(s + E_i)}{\prod_{i=1}^{n}(s + \lambda_i)} \tag{2.78}$$

The solution is (see Appendix B)

$$X_c = \sum_{\ell=1}^{n} \frac{k_{01}(1 - e^{\lambda_\ell T}) + k_{02}(e^{\lambda_\ell T} - e^{\lambda_\ell T'})}{-\lambda_\ell} \frac{\prod_{i=2}^{n}(E_i - \lambda_\ell)}{\prod_{\substack{i=1 \\ i\neq\ell}}^{n}(\lambda_i - \lambda_\ell)} e^{-\lambda_\ell t} \tag{2.79}$$

Equation (2.79) can be written in concentration terms as follows:

$$C = \sum_{\ell=1}^{n} \frac{k_{01}(1 - e^{\lambda_\ell T}) + k_{02}(e^{\lambda_\ell T} - e^{\lambda_\ell T'})}{-\lambda_\ell V_c} \frac{\prod_{i=2}^{n}(E_i - \lambda_\ell)}{\prod_{\substack{i=1 \\ i\neq\ell}}^{n}(\lambda_i - \lambda_\ell)} e^{-\lambda_\ell t} \tag{2.80}$$

When t is less than T, both T and T' are replaced by t and Eq. (2.80) reduces to Eq. (2.53). During the maintenance infusion (i.e., when $T < t < T'$), only T' is replaced by t and Eq. (2.80) may be written (on expansion) as

$$C = \sum_{\ell=1}^{n} \left[\frac{k_{01}(1 - e^{\lambda_\ell T})}{-\lambda_\ell V_c} \frac{\prod_{i=2}^{n} (E_i - \lambda_\ell)}{\prod_{\substack{i=1 \\ i\neq\ell}}^{n} (\lambda_i - \lambda_\ell)} e^{-\lambda_\ell t} + \frac{k_{02} e^{\lambda_\ell T}}{-\lambda_\ell V_c} \frac{\prod_{i=2}^{n} (E_i - \lambda_\ell)}{\prod_{\substack{i=1 \\ i\neq\ell}}^{n} (\lambda_i - \lambda_\ell)} e^{-\lambda_\ell t} + \frac{k_{02}}{\lambda_\ell V_c} \frac{\prod_{i=1}^{n} (E_i - \lambda_\ell)}{\prod_{\substack{i=1 \\ i\neq\ell}}^{n} (\lambda_i - \lambda_\ell)} \right] \tag{2.81}$$

Ultimately, as the maintenance infusion proceeds, steady state is achieved and drug concentration C_{ss} is equal to the summation of the third term on the right-hand side of Eq. (2.81). Substitution of C_{ss} for this term and rearrangement leads to an expression describing drug concentration at any time during the maintenance infusion compared to the steady-state drug concentration:

$$C - C_{ss} = \frac{1}{V_c} \sum_{\ell=1}^{n} [k_{01}(1 - e^{\lambda_\ell T}) + k_{02} e^{\lambda_\ell T}] \left[\frac{1}{-\lambda_\ell} \frac{\prod_{i=2}^{n} (E_i - \lambda_\ell)}{\prod_{\substack{i=1 \\ i\neq\ell}}^{n} (\lambda_i - \lambda_\ell)} e^{-\lambda_\ell t} \right] \tag{2.82}$$

Logically, the rate and duration of the loading infusion must be such that upon discontinuation (C_{max}, $t = T$) and initiation of the maintenance infusion, the drug concentration would exceed the desired drug concentration C_{ss}. Equation (2.82) tells us that under these conditions the time course of drug concentration may display one

of two patterns: (1) blood levels will decline but may remain above the desired drug concentration and eventually approach C_{ss}; or (2) blood levels will decline but may fall below the desired drug concentration and then slowly rise to eventually approach C_{ss}.

Wagner [13] has devised a double infusion method (with drugs acting in the central compartment in mind) that results in blood levels, at all times during the second (maintenance) infusion, greater than or equal to C_{ss}. This requires that the term $C - C_{ss}$ in Eq. (2.82) be forbidden to take on a negative value. Since the second term of the summation in (2.82) will always be negative, the first term of the summation must be negative. This, in turn, requires that

$$k_{01}e^{\lambda_\ell T} \geq k_{01} + k_{02}e^{\lambda_\ell T} \tag{2.83}$$

or

$$k_{01} \geq \frac{k_{02}}{1 - e^{-\lambda_\ell T}} \tag{2.84}$$

for all values of ℓ. An infinite number of solutions for k_{01} will satisfy the requirement imposed by (2.84), but to avoid adverse effects we seek a minimum value of k_{01}. This is found when

$$k_{01} = \frac{k_{02}}{1 - e^{-\lambda_\ell T}} \tag{2.85}$$

As noted by Vaughan and Tucker [14], Eq. (2.85) has only one solution. This is readily seen by consecutively substituting Eq. (2.85) for k_{01} in the first summation term in Eq. (2.82) using $\ell = 1, 2, 3, \ldots, n$. Since $\lambda_1 > \lambda_2 > \lambda_3 > \cdots > \lambda_n$, every value of ℓ other than $\ell = n$ will produce a positive rather than a negative value for the summation term. These outcomes violate the requirement established at the outset. Thus the appropriate rate for the loading infusion is given by

$$k_{01} = \frac{k_{02}}{1 - e^{-\lambda_n T}} \tag{2.86}$$

Under certain conditions Eq. (2.86) can be simplified to permit k_{01} to be estimated more easily. The series $e^{-x} = 1 - x + (x^2/2) - (x^3/6) + \cdots$ can be approximated accurately by $e^{-x} = 1 - x$, when $x \leq 0.1$. When this situation prevails, the denominator of (2.86) may be approximated by $\lambda_n T$ and the equation written as

$$k_{01} = \frac{k_{02}}{\lambda_n T} = \frac{1.44 k_{02} t_{1/2}}{T} \tag{2.87}$$

This approach is illustrated by the data in Fig. 2.13.

Equation (2.87) tells us that the ratio of k_{01} to k_{02} is a function of the infusion time T for the first infusion. If T is short, the ratio of infusion rates is high and relatively high blood levels will be achieved. If we increase T, we decrease the ratio of infusion rates and decrease the maximum blood level (see Fig. 2.14). The blood level at the end of the first infusion, C_{max}, may be determined by replacing t and T' in Eq. (2.80) by T. Under these conditions Eq. (2.80) reduces to

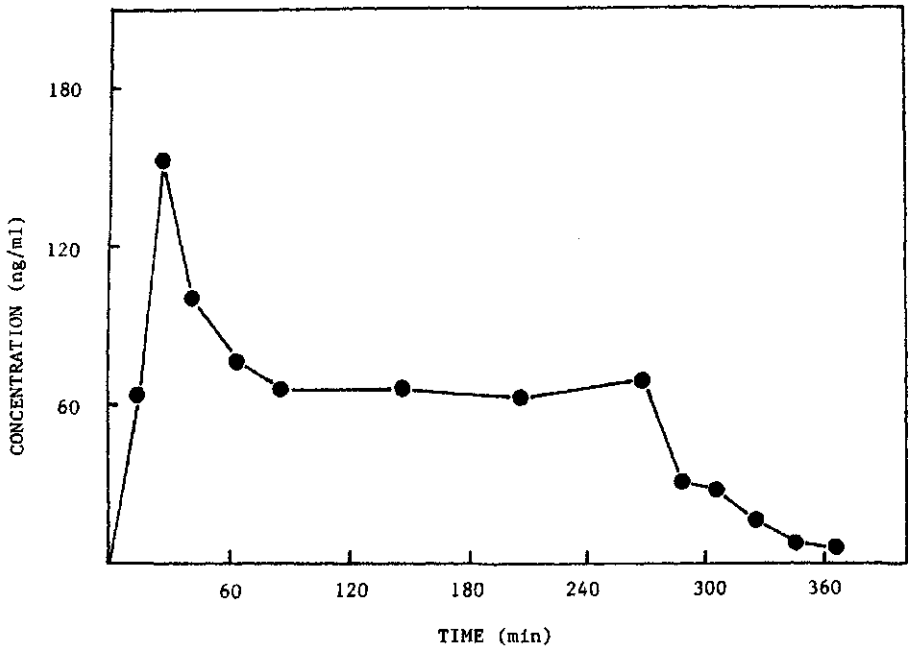


Fig. 2.13 Plot of propranolol concentration in plasma during two consecutive constant rate intravenous infusions in a representative cat. The second infusion was terminated at about 280 min. (From Ref. 15. © 1979 PJD Publications, Ltd.)

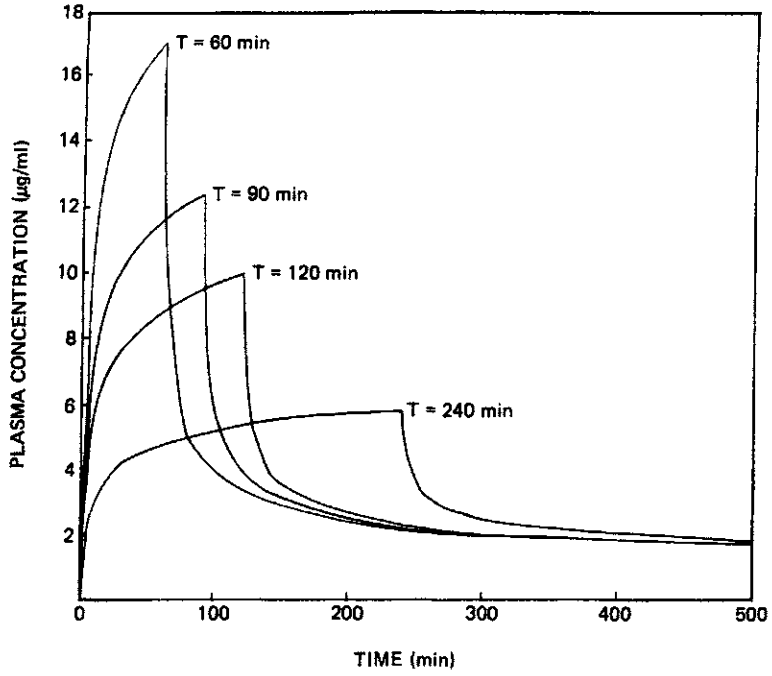


Fig. 2.14 Drug concentrations in plasma during two consecutive constant rate infusions. The maintenance infusion rate (k_{02}) was the same in each case. The loading infusion rate (k_{01}) was calculated according to Eq. (2.86), with infusion times (T) ranging from 60 to 240 min. (From Ref. 16.)

$$C_{max} = \sum_{\ell=1}^{n} \frac{k_{01}(1 - e^{\lambda_\ell T})}{-\lambda_\ell V_c} \frac{\prod_{i=2}^{n} (E_i - \lambda_\ell)}{\prod_{\substack{i=1 \\ i\neq\ell}}^{n} (\lambda_i - \lambda_\ell)} e^{-\lambda_\ell T} \tag{2.88}$$

which can be further simplified to yield

$$C_{max} = \frac{k_{01}}{V_c} \sum_{\ell=1}^{n} \frac{1 - e^{-\lambda_\ell T}}{\lambda_\ell} \frac{\prod_{i=1}^{n} (E_i - \lambda_\ell)}{\prod_{\substack{i=1 \\ i\neq\ell}}^{n} (\lambda_i - \lambda_\ell)} \tag{2.89}$$

Equation (2.89) provides a guideline for the estimation of T. After the initial selection of a desired infusion time, the maximum concentration it will produce may be determined by means of (2.89). If this value of C_{max} is inappropriately high and carries a risk of adverse effects, a longer infusion time must be considered and similarly evaluated.

FIRST-ORDER ABSORPTION

For a drug that enters the body by an apparent first-order absorption process (generally via the oral or intramuscular routes) and distributes in the body according to a multicompartment model, the disposition function for the central compartment is identical to the disposition function for an intravenous bolus injection given by (2.1):

$$d_{s,c} = \frac{\prod_{i=2}^{n} (s + E_i)}{\prod_{i=1}^{n} (s + \lambda_i)}$$

The following input function in_s is used to describe first-order absorption:

$$in_s = \frac{k_a F X_0}{s + k_a} \tag{2.90}$$

where k_a is the apparent first-order absorption rate constant and F is the fraction of the administered dose X_0 absorbed following drug administration. The Laplace transform for the amount of drug in the central compartment $a_{s,c}$ equals the product of the disposition and first-order input functions (i.e., $d_{s,c}$ and in_s), given by (2.1) and (2.90), respectively. Therefore,

$$a_{s,c} = \frac{k_a F X_0 \prod_{i=2}^{n} (s + E_i)}{(s + k_a) \prod_{i=1}^{n} (s + \lambda_i)} \tag{2.91}$$

Solving (2.91) for the amount of drug in the central compartment X_c by taking the anti-Laplace (see Appendix B) yields

$$X_c = k_a F X_0 \frac{\prod_{i=2}^{n} (E_i - k_a)}{\prod_{i=1}^{n} (\lambda_i - k_a)} e^{-k_a t} + k_a F X_0 \sum_{\ell=1}^{n} \frac{\prod_{i=2}^{n} (E_i - \lambda_\ell)}{(k_a - \lambda_\ell) \prod_{\substack{i=1 \\ i \neq \ell}}^{n} (\lambda_i - \lambda_\ell)} e^{-\lambda_\ell t} \qquad (2.92)$$

Expressing (2.92) in concentration terms employing the relationship $X_c = V_c C$ [according to (2.5)] results in the equation

$$C = \frac{k_a F X_0}{V_c} \frac{\prod_{i=2}^{n} (E_i - k_a)}{\prod_{i=1}^{n} (\lambda_i - k_a)} e^{-k_a t} + \frac{k_a F X_0}{V_0} \sum_{\ell=1}^{n} \frac{\prod_{i=2}^{n} (E_i - \lambda_\ell)}{(k_a - \lambda_\ell) \prod_{\substack{i=1 \\ i \neq \ell}}^{n} (\lambda_i - \lambda_\ell)} e^{-\lambda_\ell t} \qquad (2.93)$$

The absorption rate constant, for most drugs administered in readily available dosage forms, is probably significantly larger than the terminal disposition rate constant λ_n, and since by definition λ_1 to λ_{n-1} are larger than λ_n, at some time following administration the terms $e^{-k_a t}$ and $e^{-\lambda_1 t}$ to $e^{-\lambda_{n-1} t}$ approach zero and (2.93) reduces to

$$C = \frac{k_a F X_0}{V_c} \frac{\prod_{i=2}^{n} (E_i - \lambda_n)}{(k_a - \lambda_n) \prod_{\substack{i=1 \\ i \neq n}}^{n} (\lambda_i - \lambda_n)} e^{-\lambda_n t} \qquad (2.94)$$

Therefore, a plot of the logarithm of plasma concentration versus time following first-order input into a multicompartment model yields a multiexponential curve (Fig. 2.15), the terminal portion of which is

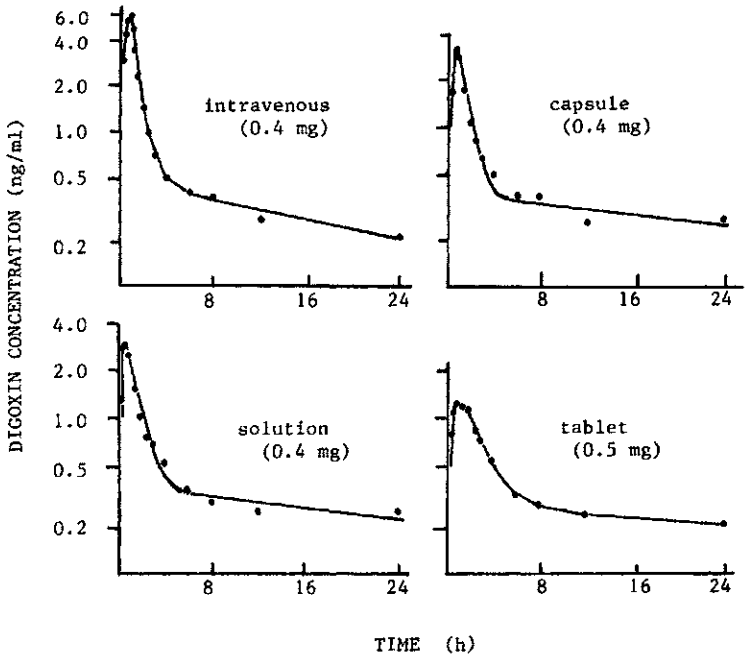


Fig. 2.15 Average digoxin concentrations in plasma after administration of an intravenous dose or an oral dose in one of three formulations to 12 healthy volunteers. The multicompartment characteristics of digoxin are evident after oral as well as after intravenous administration. (From Ref. 17.)

linear and described by (2.94). An estimate of the terminal disposition rate constant can be obtained from the slope, $\lambda_n/2.303$, of this terminal linear segment.

Following oral administration of many drugs that display multicompartment characteristics after intravenous injection, we often fail to observe a distributive phase. The plasma concentration-time curves for such drugs appear biexponential rather than multiexponential (i.e., such curves behave as if the drug in question confers on the body one-compartment rather than multicompartment characteristics). It has been illustrated through simulations, assuming a two-compartment model (i.e., n = 2), that as k_a approaches λ_1, data will still yield a curve consistent with a multicompartment system as illustrated in Fig. 2.15, even though the two exponentials are approximately equal to each other [18]. However, when k_a approaches E_2, the data are best fit by a one-compartment model. Therefore, the predominant distributive phase in Fig. 2.15 is characteristic of a multi-

compartment model where k_a is larger than E_2 and larger than or approaching λ_1.

Pharmacokinetic analysis of the blood level-time curve following an administration requiring first-order input (by the method of residuals, Appendix C, or nonlinear least-squares regression analysis, Appendix H), to obtain k_a and the disposition rate constants λ_1 to λ_n may not be possible without intravenous data, since such data are usually necessary for gaining an appreciation of the relative magnitudes of these rate constants. Assuming that the rate constant determined from the terminal slope is λ_n, λ_1 will be the rate constant calculated from the residual line if the data are best fit by a one-compartment model. When a one-compartment model adequately describes the data, k_a approaches E_2. As can be seen in (2.93), this causes the coefficient of the exponential term describing absorption to approach zero. If the data are multicompartmental in nature, it is not possible to predict whether the larger rate constant obtained from the residual lines should be assigned to k_a or to λ_1. As k_a approaches or becomes less than λ_n (i.e., a flip-flop model), the resulting plasma concentration versus time plot again defies analysis, since one cannot unambiguously assign the slow rate constant to either k_a or λ_n without intravenous data.

DETERMINATION OF PHARMACOKINETIC PARAMETERS

Calculation of k_{10}, k_{12}, k_{21}, and k_e'

Two-Compartment Model, Elimination Central. The disposition function $d_{s,c}$ for the central compartment of an n-compartment mammillary model [given by Eq. (2.1)] can also be written as follows (see Appendix B):

$$d_{s,c} = \frac{\prod_{i=2}^{n} (s + E_i)}{\prod_{i=1}^{n} (s + E_i) - \sum_{j=2}^{n} \left[k_{1j}k_{j1} \prod_{\substack{m=2 \\ m\neq j}}^{n} (s + E_m)\right]} \tag{2.95}$$

where k_{1j} and k_{j1} are first-order intercompartmental transfer rate constants, and E_i and E_m are the sum of the first-order exit rate constants out of compartment i or m. If the simplest case is considered (i.e., where a plasma concentration versus time curve is described by a biexponential equation), n will equal 2 (i.e., a two-compartment mammillary model; see Fig. 2.3) and (2.95) becomes

$$d_{s,c} = \frac{s + E_2}{(s + E_1)(s + E_2) - k_{12}k_{21}} \tag{2.96}$$

where $E_1 = k_{10} + k_{12}$ and $E_2 = k_{21}$. The constant k_{10} is the apparent first-order elimination rate constant from the central compartment, and k_{12} and k_{21} are the intercompartmental transfer rate constants (see Fig. 2.3). Expansion of the denominators of (2.96) and (2.1), when n = 2, yields

$$d_{s,c} = \frac{s + E_2}{s^2 + s(E_1 + E_2) + E_1E_2 - k_{12}k_{21}} \tag{2.97}$$

and

$$d_{s,c} = \frac{s + E_2}{s^2 + s(\lambda_1 + \lambda_2) + \lambda_1\lambda_2} \tag{2.98}$$

respectively. By comparing (2.97) and (2.98) it can be shown that $\lambda_1 + \lambda_2 = E_1 + E_2$ and $\lambda_1\lambda_2 = E_1E_2 - k_{12}k_{21}$. Substitution of $k_{10} + k_{12}$ for E_1 and k_{21} for E_2 yields the following equations for λ_1 and λ_2:

$$\lambda_1 + \lambda_2 = k_{10} + k_{12} + k_{21} \tag{2.99}$$

and

$$\lambda_1\lambda_2 = k_{10}k_{21} \tag{2.100}$$

λ_1 is by definition greater than λ_2.

The specific equation that describes the biexponential decay in plasma concentrations following the intravenous bolus injection of a drug can be readily obtained by setting n = 2 in (2.7):

$$C = A_1e^{-\lambda_1 t} + A_2e^{-\lambda_2 t} \tag{2.101}$$

where A_1 and A_2 are given by [see (2.8)]

$$A_1 = \frac{X_0(E_2 - \lambda_1)}{V_c(\lambda_2 - \lambda_1)} = \frac{X_0(k_{21} - \lambda_1)}{V_c(\lambda_2 - \lambda_1)} \tag{2.102}$$

and

$$A_2 = \frac{X_0(E_2 - \lambda_2)}{V_c(\lambda_1 - \lambda_2)} = \frac{X_0(k_{21} - \lambda_2)}{V_c(\lambda_1 - \lambda_2)} \tag{2.103}$$

The terms λ_1, λ_2, A_1, and A_2 are commonly referred to as α, β, A, and B in the literature.

As discussed previously in this chapter λ_1, λ_2, A_1, and A_2 are generally obtained from the nonlinear least-squares fit of plasma concentration versus time data to Eq. (2.101) (Appendix H). Once these

parameters are determined, the constants k_{10}, k_{12}, and k_{21} can be calculated. The apparent volume of the central compartment, V_c, is given by (2.15) when n = 2:

$$V_c = \frac{X_0}{A_1 + A_2} \tag{2.104}$$

Substitution of $A_1 + A_2$ for X_0/V_c [obtained by rearrangement of (2.104)] in (2.103) yields

$$A_2 = \frac{(A_1 + A_2)(k_{21} - \lambda_2)}{\lambda_1 - \lambda_2} \tag{2.105}$$

which can be solved for k_{21}, since

$$k_{21} = \frac{A_1\lambda_2 + A_2\lambda_1}{A_1 + A_2} \tag{2.106}$$

The elimination rate constant from the central compartment can now be calculated since k_{21} is known (2.106) and $\lambda_1\lambda_2 = k_{10}k_{21}$ (2.100). Hence

$$k_{10} = \frac{\lambda_1\lambda_2}{k_{21}} \tag{2.107}$$

Recalling that $\lambda_1 + \lambda_2 = k_{10} + k_{12} + k_{21}$ (2.99), it follows that

$$k_{12} = \lambda_1 + \lambda_2 - k_{21} - k_{10} \tag{2.108}$$

All of these parameters, namely V_c, k_{10}, k_{12}, and k_{21}, can also be obtained from postinfusion data when the appropriate values of A_ℓ have been determined from the values of R_ℓ using Eqs. (2.69) and (2.72).

These constants may also be obtained from urinary excretion data. The following equation will describe the biexponential decline in an excretion rate versus time plot [set n = 2 in (2.23)]:

$$\frac{dX_u}{dt} = A_1'e^{-\lambda_1 t} + A_2'e^{-\lambda_2 t} \tag{2.109}$$

where

$$A_1' = k_e'X_0\frac{E_2 - \lambda_1}{\lambda_2 - \lambda_1} = k_e'X_0\frac{k_{21} - \lambda_1}{\lambda_2 - \lambda_1} \tag{2.110}$$

and

$$A_2' = k_e'X_0\frac{E_2 - \lambda_2}{\lambda_1 - \lambda_2} = k_e'X_0\frac{k_{21} - \lambda_2}{\lambda_1 - \lambda_2} \tag{2.111}$$

are obtained from (2.24). Rearrangement of (2.111) yields

$$k_{21} = \frac{A'_2(\lambda_1 - \lambda_2)}{k'_e X_0} + \lambda_2 \tag{2.112}$$

The parameter k'_e, the first-order urinary excretion rate constant, can be obtained for a two-compartment model from (2.27):

$$k'_e = \frac{A'_1 + A'_2}{X_0} \tag{2.113}$$

Substitution for k'_e in (2.112) according to (2.113) gives

$$k_{21} = \frac{A'_2(\lambda_1 - \lambda_2)X_0}{(A'_1 + A'_2)X_0} + \lambda_2 \tag{2.114}$$

Canceling the X_0 terms and solving for a common denominator yields

$$k_{21} = \frac{A'_2\lambda_1 - A'_2\lambda_2 + A'_1\lambda_2 + A'_2\lambda_2}{A'_1 + A'_2} \tag{2.115}$$

which when simplified becomes

$$k_{21} = \frac{A'_2\lambda_1 + A'_1\lambda_2}{A'_1 + A'_2} \tag{2.116}$$

and is analogous to (2.106). The constants k_{10} and k_{12} can be solved for by employing the value of k_{21} from (2.114), and utilizing Eqs. (2.107) ($k_{10} = \lambda_1\lambda_2/k_{21}$) and (2.108) ($k_{12} = \lambda_1 + \lambda_2 - k_{21} - k_{10}$).

Amount unexcreted in the urine versus time data can also be used to determine k_{10}, k_{12}, and k_{21}. By setting n = 2 in (2.33), the following equation results:

$$X_u^\infty - X_u = A''_1 e^{-\lambda_1 t} + A''_2 e^{-\lambda_2 t} \tag{2.117}$$

where

$$A''_1 = k'_e X_0 \frac{E_1 - \lambda_1}{\lambda_1(\lambda_2 - \lambda_1)} = k'_e X_0 \frac{k_{21} - \lambda_1}{\lambda_1(\lambda_2 - \lambda_1)} \tag{2.118}$$

and

$$A''_2 = k'_e X_0 \frac{E_2 - \lambda_2}{\lambda_2(\lambda_1 - \lambda_2)} = k'_e X_0 \frac{k_{21} - \lambda_2}{\lambda_2(\lambda_1 - \lambda_2)} \tag{2.119}$$

are obtained from (2.34) by setting n = 2. Setting n = 2 in (2.31) and solving for k'_e yields

$$k'_e = \frac{X_u^\infty \lambda_1 \lambda_2}{X_0 E_2} = \frac{X_u^\infty \lambda_1 \lambda_2}{X_0 k_{21}} \tag{2.120}$$

Substitution of $k_{10}k_{21}$ for $\lambda_1\lambda_2$ in (2.120) according to (2.100) and cancellation of common terms provides

$$k'_e = \frac{X_u^\infty k_{10}}{X_0} \tag{2.121}$$

Multiplying the numerator and denominator of (2.119) by λ_1 and expanding the numerator gives

$$A''_2 = k'_e X_0 \frac{\lambda_1 k_{21} - \lambda_1 \lambda_2}{\lambda_1 \lambda_2 (\lambda_1 - \lambda_2)} \tag{2.122}$$

The substitution of $k_{10}k_{21}$ for $\lambda_1\lambda_2$ in this equation followed by cancellation of the common parameter k_{21} yields

$$A''_2 = \frac{k'_e X_0 (\lambda_1 - k_{10})}{k_{10}(\lambda_1 - \lambda_2)} \tag{2.123}$$

X_u^∞ can be substituted for $k'_e X_0 / k_{10}$ in (2.123) based on a rearrangement of (2.121) to give

$$A''_2 = X_u^\infty \frac{\lambda_1 - k_{10}}{\lambda_1 - \lambda_2} \tag{2.124}$$

It can be readily shown from (2.117) that

$$X_u^\infty = A''_1 + A''_2 \tag{2.125}$$

Substituting $A''_1 + A''_2$ for X_u^∞ in (2.124) and solving for k_{10} yields

$$k_{10} = \frac{A''_1 \lambda_1 + A'' \lambda_2}{A''_1 + A''_2} \tag{2.126}$$

The constant k_{21} can be obtained by rearranging (2.100) to give

$$k_{21} = \frac{\lambda_1 \lambda_2}{k_{10}} \tag{2.127}$$

while Eq. (2.108) can be used to calculate k_{12}.

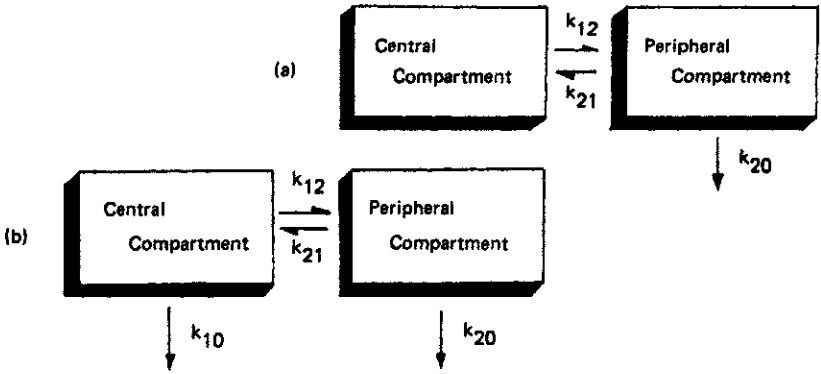


Fig. 2.16 Schematic representation of the body as a two-compartment open model. In case (a), elimination is restricted to the peripheral compartment; in case (b), elimination occurs from both compartments.

Two-Compartment Model, Elimination Peripheral or Central and Peripheral. Elimination in a two-compartment model may occur not only from the central compartment but also from the peripheral compartment or from both compartments simultaneously (Fig. 2.16). Although the three two-compartment models are indistinguishable based solely on plasma or urinary excretion data, additional information may be available that will require the use of one of the models in which elimination is not exclusive to the central compartment.

For the case where elimination occurs only from the peripheral compartment, the following disposition function for the central compartment, $d_{s,c}$, may be written [see (2.95)]:

$$d_{s,c} = \frac{s + E_2}{(s + E_1)(s + E_2) - k_{12}k_{21}} \tag{2.96}$$

However, $E_1 = k_{12}$ and $E_2 = k_{21} + k_{20}$ (see Fig. 2.16a), where k_{20} is the apparent first-order elimination rate constant from the peripheral compartment. The constants k_{12} and k_{21} are as defined previously. Since there are two driving force compartments in the model, (2.96) may also be written as

$$d_{s,c} = \frac{s + E_2}{(s + \lambda_1)(s + \lambda_2)} \tag{2.128}$$

Expansion of (2.96) and (2.128) yields (2.97) and (2.98), respectively, and $\lambda_1 + \lambda_2$ equals $E_1 + E_2$ and $\lambda_1\lambda_2$ equals $E_1E_2 - k_{12}k_{21}$. Substitution of k_{12} for E_1 and $k_{21} + k_{20}$ for E_2 yields the following expressions for λ_1 and λ_2:

$$\lambda_1 + \lambda_2 = k_{12} + k_{21} + k_{20} \tag{2.129}$$

and

$$\lambda_1\lambda_2 = k_{12}k_{20} \tag{2.130}$$

For intravenous administration the input function in_s equals X_0, the intravenous dose [Eq. (2.2)]. The Laplace transform for the amount of drug in the central compartment, $a_{s,c}$, is therefore

$$a_{s,c} = \frac{(s + E_2)X_0}{(s + \lambda_1)(s + \lambda_2)} \tag{2.131}$$

where $a_{s,c}$ equals the product of $d_{s,c}$ and in_s, E_2 equals $k_{21} + k_{20}$, and λ_1 and λ_2 are defined by (2.129) and (2.130). The anti-Laplace of this equation yields an expression for the amount of drug in the central compartment (X_c) as a function of time, which is

$$X_c = \frac{X_0(E_2 - \lambda_1)}{\lambda_2 - \lambda_1} e^{-\lambda_1 t} + \frac{X_0(E_2 - \lambda_2)}{\lambda_1 - \lambda_2} e^{-\lambda_2 t} \tag{2.132}$$

Substituting $k_{21} + k_{20}$ for E_2, converting to concentration terms employing Eq. (2.5) ($X_c = V_c C$), and rearranging yields

$$C = \frac{X_0(\lambda_1 - k_{21} - k_{20})}{V_c(\lambda_1 - \lambda_2)} e^{-\lambda_1 t} + \frac{X_0(k_{21} + k_{20} - \lambda_2)}{V_c(\lambda_1 - \lambda_2)} e^{-\lambda_2 t} \tag{2.133}$$

or

$$C = A_1 e^{-\lambda_1 t} + A_2 e^{-\lambda_2 t}$$

which is identical to Eq. (2.101). However,

$$A_1 = \frac{X_0(\lambda_1 - k_{21} - k_{20})}{V_c(\lambda_1 - \lambda_2)} \tag{2.134}$$

and

$$A_2 = \frac{X_0(k_{21} + k_{20} - \lambda_2)}{V_c(\lambda_1 - \lambda_2)} \tag{2.135}$$

From a plot of log C versus time, estimates of A_1, A_2, λ_1, and λ_2 can be made (method of residuals, Appendix C; nonlinear regression analysis, Appendix H) from which V_c, k_{12}, k_{21}, and k_{20} can be determined.

The apparent volume of the central compartment can be estimated employing Eq. (2.104):

$$V_c = \frac{X_0}{A_1 + A_2}$$

where A_1 and A_2 are as defined by (2.134) and (2.135), respectively. Substitution of $A_1 + A_2$ for X_0/V_c [Eq. (2.104)] into (2.135) yields

$$A_1 = \frac{(A_1 + A_2)(k_{21} + k_{20} - \lambda_2)}{\lambda_1 - \lambda_2} \tag{2.136}$$

Equation (2.99) can be rearranged to give

$$k_{21} + k_{20} - \lambda_2 = \lambda_1 - k_{12} \tag{2.137}$$

Substituting $\lambda_1 - k_{12}$ for $k_{21} + k_{20} - \lambda_2$ into (2.136) and rearranging gives the following expression which can be employed to calculate k_{12}:

$$k_{12} = \frac{\lambda_1 A_1 + \lambda_2 A_2}{A_1 + A_2} \tag{2.138}$$

The elimination rate constant from the peripheral compartment, k_{20}, can now be calculated since k_{12} is known [Eq. (2.138)] and since $\lambda_1\lambda_2 = k_{12}k_{20}$ [Eq. (2.130)]. Rearranging (2.130) yields the following expression for k_{20}:

$$k_{20} = \frac{\lambda_1\lambda_2}{k_{12}} \tag{2.139}$$

The constant k_{21} can now be determined by rearrangement of (2.99) to yield

$$k_{21} = \lambda_1 + \lambda_2 - k_{12} - k_{20} \tag{2.140}$$

The third type of two-compartment model, where elimination occurs from both the central and peripheral compartments (Fig. 2.16b), may be solved in a manner analogous to the other two-compartment models. A biexponential equation of the form $C = A_1e^{-\lambda_1 t} + A_2e^{-\lambda_2 t}$ will result. Relationships can be derived employing the methods and approaches developed above which relate the individual model constants k_{12}, k_{21}, k_{10}, and k_{20} to the hybrid constants λ_1, λ_2, A_1, and A_2. However, none of the model constants can be calculated independently, since in a mammillary disposition model, the maximum number of solvable rate constants Z is given by the following equation [5]:

$$Z = 2(n - 1) + 1 \tag{2.141}$$

where n is the number of driving force compartments in the disposition model. There are two driving force compartments in any two-compart-

ment model and therefore the maximum number of solvable rate constants is three. The model shown in Fig. 2.16b has four rate constants.

Three-Compartment Model. Triexponential equations may be required to describe adequately postintravenous injection data. In accordance with previous discussions, the simplest three-compartment model will be considered: that model where elimination occurs from a central compartment which is reversibly connected to a "shallow" and a "deep" peripheral compartment, compartments 2 and 3, respectively (Fig. 2.17).

The disposition function for the central compartment, $d_{s,c}$, may be obtained by setting n = 3 in (2.1) or (2.95). This will yield

$$d_{s,c} = \frac{(s + E_2)(s + E_3)}{(s + \lambda_1)(s + \lambda_2)(s + \lambda_3)} \tag{2.142}$$

and

$$d_{s,c} = \frac{(s + E_2)(s + E_3)}{(s + E_1)(s + E_2)(s + E_3) - k_{12}k_{21}(s + E_3) - k_{13}k_{31}(s + E_2)} \tag{2.143}$$

respectively, where $E_2 = k_{21}$, $E_3 = k_{31}$, and $E_1 = k_{12} + k_{13} + k_{10}$. The constants k_{12} and k_{21}, and k_{31} and k_{13} are the apparent first-order intercompartmental transfer rate constants between the shallow and central compartments, and deep and central compartments, respectively. The elimination rate constant from the central compartment is k_{10}. In (2.142) λ_1 is by definition greater than λ_2, which is in turn greater than λ_3.

Substituting k_{21} for E_2 and k_{31} for E_3 in (2.142) and (2.143) and $k_{12} + k_{13} + k_{10}$ for E_1 in (2.143) and expanding the denominators of (2.142) and (2.143) yields

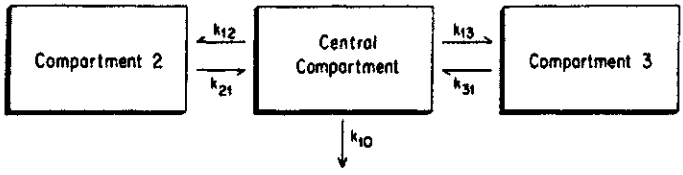


Fig. 2.17 Schematic representation of the body as a three-compartment open model with drug elimination from the central compartment.

$$d_{s,c} = \frac{(s + k_{21})(s + k_{31})}{s^3 + s^2(\lambda_1 + \lambda_2 + \lambda_3) + s(\lambda_1\lambda_2 + \lambda_1\lambda_3 + \lambda_2\lambda_3) + \lambda_1\lambda_2\lambda_3} \tag{2.144}$$

and

$$d_{s,c} = \frac{(s + k_{21})(s + k_{31})}{s^3 + s^2(k_{10} + k_{12} + k_{13} + k_{21} + k_{31}) + s(k_{10}k_{21} + k_{13}k_{21} + k_{10}k_{31} + k_{21}k_{31} + k_{31}k_{12}) + k_{21}k_{31}k_{10}} \tag{2.145}$$

respectively. Comparing the coefficients in the denominators of (2.144) and (2.145), it is readily apparent that λ_1, λ_2, and λ_3 may be expressed in terms of the individual rate constants as

$$\lambda_1 + \lambda_2 + \lambda_3 = k_{10} + k_{12} + k_{13} + k_{21} + k_{31} \tag{2.146}$$

$$\lambda_1\lambda_2 + \lambda_1\lambda_3 + \lambda_2\lambda_3 = k_{10}k_{21} + k_{13}k_{21} + k_{10}k_{31} + k_{21}k_{31} + k_{31}k_{12} \tag{2.147}$$

and

$$\lambda_1\lambda_2\lambda_3 = k_{21}k_{31}k_{10} \tag{2.148}$$

The intravenous input function in_s is given by Eq. (2.2), that is, $in_s = X_0$, where X_0 is the intravenous dose. The Laplace transform for the amount of drug in the central compartment, $a_{s,c}$, which is the product of the input and disposition functions [given by (2.2) and (2.142), respectively], is

$$a_{s,c} = \frac{X_0(s + E_2)(s + E_3)}{(s + \lambda_1)(s + \lambda_2)(s + \lambda_3)} \tag{2.149}$$

Taking the anti-Laplace of (2.149) (Appendix B) yields the following expression for the amount of drug in the central compartment, X_c, as a function of time:

$$X_c = \frac{X_0(E_2 - \lambda_1)(E_3 - \lambda_1)}{(\lambda_2 - \lambda_1)(\lambda_3 - \lambda_1)} e^{-\lambda_1 t} + \frac{X_0(E_2 - \lambda_2)(E_3 - \lambda_2)}{(\lambda_1 - \lambda_2)(\lambda_3 - \lambda_2)} e^{-\lambda_2 t} + \frac{X_0(E_2 - \lambda_3)(E_3 - \lambda_3)}{(\lambda_1 - \lambda_3)(\lambda_2 - \lambda_3)} e^{-\lambda_3 t} \tag{2.150}$$

Substituting k_{31} for E_3, and k_{21} for E_2, rearranging, and expressing the equation in concentration terms by dividing by V_c according to (2.5) ($C = X_c/V_c$) yields

$$C = \frac{X_0(k_{21} - \lambda_1)(k_{31} - \lambda_1)}{V_c(\lambda_1 - \lambda_2)(\lambda_1 - \lambda_3)} e^{-\lambda_1 t} + \frac{X_0(k_{21} - \lambda_2)(\lambda_2 - k_{31})}{V_c(\lambda_1 - \lambda_2)(\lambda_2 - \lambda_3)} e^{-\lambda_2 t}$$
$$+ \frac{X_0(k_{21} - \lambda_3)(k_{31} - \lambda_3)}{V_c(\lambda_2 - \lambda_3)(\lambda_1 - \lambda_3)} e^{-\lambda_3 t} \qquad (2.151)$$

or

$$C = A_1 e^{-\lambda_1 t} + A_2 e^{-\lambda_2 t} + A_3 e^{-\lambda_3 t} \qquad (2.152)$$

where

$$A_1 = \frac{X_0(k_{21} - \lambda_1)(k_{31} - \lambda_1)}{V_c(\lambda_1 - \lambda_2)(\lambda_1 - \lambda_3)} \qquad (2.153)$$

$$A_2 = \frac{X_0(k_{21} - \lambda_2)(\lambda_2 - k_{31})}{V_c(\lambda_1 - \lambda_2)(\lambda_2 - \lambda_3)} \qquad (2.154)$$

and

$$A_3 = \frac{X_0(k_{21} - \lambda_3)(k_{31} - \lambda_3)}{V_c(\lambda_2 - \lambda_3)(\lambda_1 - \lambda_3)} \qquad (2.155)$$

Therefore, from a plot of the logarithm of plasma concentration versus time after rapid intravenous injection, a triexponential curve should be obtained from which A_1, A_2, A_3, λ_1, λ_2, and λ_3 can be estimated (Fig. 2.18). Although such estimations can be made employing the method of residuals (Appendix C), the best method to determine these terms is to fit the curve by nonlinear least-squares regression analysis (Appendix H).

Once A_1, A_2, A_3, λ_1, λ_2, and λ_3 are known, the apparent volume of the central compartment V_c and the individual rate constants k_{12}, k_{21}, k_{13}, k_{31}, and k_{10} can be calculated. At time $t = 0$ the plasma concentration C_0 is given by the equation

$$C_0 = A_1 + A_2 + A_3 \qquad (2.156)$$

Substitution for A_1, A_2, and A_3 according to (2.153), (2.154), and (2.155), respectively, in Eq. (2.156), bringing the resulting expression to a common denominator, expanding the numerator and denominator, and simplifying yields Eq. 2.14

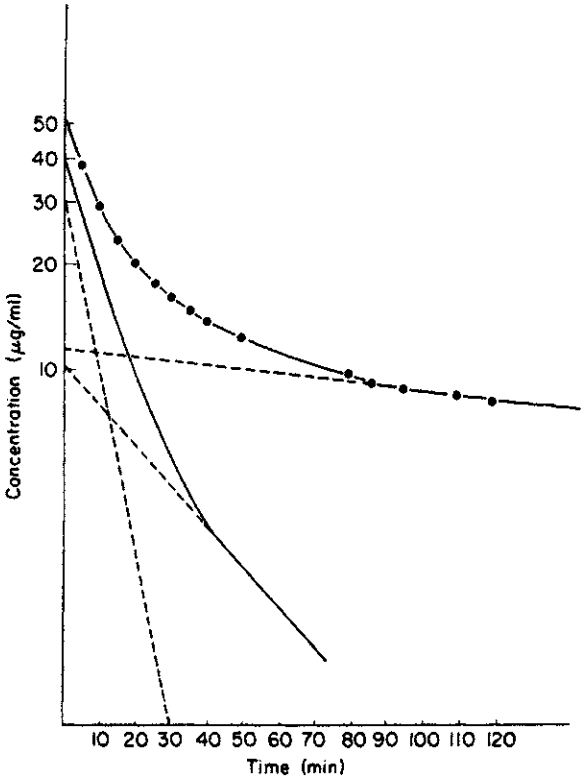


Fig. 2.18 Dacarbazine concentration in plasma following intravenous administration in the dog. Application of the method of residuals indicates that the data are described by the following triexponential equation: $C = 30.5 \exp(-0.117t) + 10.2 \exp(-0.028t) + 11.4 \exp(-0.003t)$, where t is expressed in minutes. (Data from Ref. 19.)

$$C_0 = \frac{X_0}{V_c}$$

Substitution of $A_1 + A_2 + A_3$ for C_0, according to (2.156), in (2.14) and rearrangement yields the following expression for V_c:

$$V_c = \frac{X_0}{A_1 + A_2 + A_3} \tag{2.157}$$

By substituting $A_1 + A_2 + A_3$ for X_0/V_c in (2.154) and (2.155), and solving (2.154) for k_{21} and (2.155) for k_{31}, the following relationships are obtained:

$$k_{21} = \lambda_2 + \frac{A_2(\lambda_1 - \lambda_2)(\lambda_2 - \lambda_3)}{(A_1 + A_2 + A_3)(\lambda_2 - k_{31})} \tag{2.158}$$

and

$$k_{31} = \lambda_3 + \frac{A_3(\lambda_1 - \lambda_3)(\lambda_2 - \lambda_3)}{(A_1 + A_2 + A_3)(k_{21} - \lambda_3)} \tag{2.159}$$

respectively. Substitution of k_{21}, according to (2.158), in (2.159) and simplification yields the following quadratic equation:

$$k_{31}^2 - k_{31}\frac{\lambda_1A_3 + \lambda_1A_2 + \lambda_3A_1 + \lambda_3A_2 + \lambda_2A_1 + \lambda_2A_3}{A_1 + A_2 + A_3} + \frac{\lambda_1\lambda_2A_3 + \lambda_1\lambda_3A_2 + \lambda_2\lambda_3A_1}{A_1 + A_2 + A_3} = 0 \tag{2.160}$$

Similarly, substituting for k_{31}, according to (2.159), in (2.158) and simplifying yields a quadratic equation in k_{21} with identical coefficients:

$$k_{21}^2 - k_{21}\frac{\lambda_1A_3 + \lambda_1A_2 + \lambda_3A_1 + \lambda_3A_2 + \lambda_2A_1 + \lambda_2A_3}{A_1 + A_2 + A_3} + \frac{\lambda_1\lambda_2A_3 + \lambda_1\lambda_3A_2 + \lambda_2\lambda_3A_1}{A_1 + A_2 + A_3} = 0 \tag{2.161}$$

Equations (2.160) and (2.161) are of the form $ax^2 + bx + c = 0$, which may be solved by

$$x = \frac{-b \pm \sqrt{b^2 - 4ac}}{2a} \tag{2.162}$$

Therefore,

$$k_{21},\ k_{31} = \frac{-b \pm \sqrt{b^2 - 4ac}}{2a} \tag{2.163}$$

where

$$a = 1 \tag{2.164}$$

$$b = -\frac{\lambda_1A_3 + \lambda_1A_2 + \lambda_3A_1 + \lambda_3A_2 + \lambda_2A_1 + \lambda_2A_3}{A_1 + A_2 + A_3} \tag{2.165}$$

and

$$c = \frac{\lambda_1\lambda_2A_3 + \lambda_1\lambda_3A_2 + \lambda_2\lambda_3A_1}{A_1 + A_2 + A_3} \tag{2.166}$$

Since k_{31} is the exit rate constant from the deep peripheral compartment, it will be smaller than k_{21}, the exit rate constant from the shallow peripheral compartment. Hence

$$k_{31} = \frac{1}{2}\left(-b - \sqrt{b^2 - 4c}\right) \tag{2.167}$$

and

$$k_{21} = \frac{1}{2}\left(-b + \sqrt{b^2 - 4c}\right) \tag{2.168}$$

Once k_{31} and k_{21} have been determined, the elimination rate constant from the central compartment k_{10} can be readily calculated from

$$k_{10} = \frac{\lambda_1\lambda_2\lambda_3}{k_{21}k_{31}} \tag{2.169}$$

which is obtained by rearrangement of (2.148).

Solving (2.146) and (2.147) for k_{13} yields

$$k_{13} = (\lambda_1 + \lambda_2 + \lambda_3) - (k_{10} + k_{21} + k_{31} + k_{12}) \tag{2.170}$$

and

$$k_{13} = \frac{(\lambda_1\lambda_3 + \lambda_1\lambda_2 + \lambda_1\lambda_3) - (k_{10}k_{21} + k_{10}k_{31} + k_{21}k_{31} + k_{12}k_{31})}{k_{21}} \tag{2.171}$$

respectively. By subtracting (2.170) from (2.171) and solving for k_{12}, the following expression is obtained:

$$k_{12} = \frac{(\lambda_2\lambda_3 + \lambda_1\lambda_2 + \lambda_1\lambda_3) - k_{21}(\lambda_1 + \lambda_2 + \lambda_3) - k_{10}k_{31} + k_{21}^2}{k_{31} - k_{21}} \tag{2.172}$$

Rearrangement of (2.146) yields

$$k_{13} = \lambda_1 + \lambda_2 + \lambda_3 - (k_{10} + k_{12} + k_{21} + k_{31}) \tag{2.173}$$

from which k_{13} can be calculated since the constants k_{10}, k_{12}, k_{21}, and k_{31} are known.

As with a two-compartment model, there are many types of three-compartment models where elimination may be assumed to occur from any one compartment or combination of compartments. These models

are indistinguishable based solely on plasma or urinary excretion data. There are indications that a triexponential equation may be necessary to characterize the pharmacokinetic profile of digoxin [20], tubocurarine [21], 5-(dimethyltriazeno)imidazole-4-carboxamide [19], and diazepam [22]. A three-compartment model involving peripheral compartment elimination has been employed for bishydroxycoumarin [23]. The derivation for this particular model is given therein.

Determination of the rate constants associated with multicompartment models may permit an assessment of the relative contribution of distribution and elimination processes to the drug concentration versus time profile of a drug. It may also aid in elucidating the mechanism of drug interactions, and of the effects of disease, age, genetic influences, and other factors on drug disposition. However, it must be kept in mind that these parameters are likely to be subject to considerable error. As pointed out by Westlake [24], these errors are probably unimportant when the parameters are used to predict plasma drug concentration. If the parameters are used to predict other features of the system (e.g., tissue drug concentrations), there may be substantial errors in the predictions.

Relationship Between β *and* k_{10}. For multicompartment models a clear distinction must be made between k_{10}, the elimination rate constant, and the terminal disposition rate constant λ_n, which is frequently referred to as β in the literature. λ_n or β is equivalent to λ_2 or λ_3 in the respective bi- or triexponential equations discussed above. The difference between k_{10} and λ_n may be clearly illustrated employing the simplest multiexponential equation, the biexponential equation. These two constants may be related in the following manner. The fraction of drug in the body that is in the central compartment, f_c, can be defined as

$$f_c = \frac{X_c}{X} \tag{2.174}$$

where X is the total amount of drug in the body and equals the sum of the amounts of drug in the central and peripheral body compartments:

$$X = X_c + X_p \tag{2.175}$$

Substitution of $X_c + X_p$ for X in (2.174) gives

$$f_c = \frac{X_c}{X_c + X_p} \tag{2.176}$$

The appropriate values of X_c and X_p can be obtained from (2.4) and (2.19), respectively. Setting n and j in these equations equal to 2,

which results in biexponential equations, then substituting these equations for X_c and X_p in (2.176), yields

$$f_c = \frac{X_0 \frac{E_2 - \lambda_1}{\lambda_2 - \lambda_1} e^{-\lambda_1 t} + X_0 \frac{E_2 - \lambda_2}{\lambda_1 - \lambda_2} e^{-\lambda_2 t}}{X_0 \frac{E_2 - \lambda_1}{\lambda_2 - \lambda_1} e^{-\lambda_1 t} + X_0 \frac{E_2 - \lambda_2}{\lambda_1 - \lambda_2} e^{-\lambda_2 t} + X_0 \frac{k_{12}(E_2 - \lambda_1)}{(E_2 - \lambda_1)(\lambda_2 - \lambda_1)} e^{-\lambda_1 t} + X_0 \frac{k_{12}(E_2 - \lambda_2)}{(E_2 - \lambda_2)(\lambda_1 - \lambda_2)} e^{-\lambda_2 t}} \tag{2.177}$$

Initial canceling of common terms and changing all coefficients to a common denominator, $\lambda_1 - \lambda_2$, which can then be canceled, gives

$$f_c = \frac{(\lambda_1 - E_2)e^{-\lambda_1 t} + (E_2 - \lambda_2)e^{-\lambda_2 t}}{(\lambda_1 - E_2)e^{-\lambda_1 t} + (E_2 - \lambda_2)e^{-\lambda_2 t} - k_{12}e^{-\lambda_1 t} + k_{12}e^{-\lambda_2 t}} \tag{2.178}$$

Substituting k_{21} for E_2 and collecting common terms in the denominator results in the following equation:

$$f_c = \frac{(\lambda_1 - k_{21})e^{-\lambda_1 t} + (k_{21} - \lambda_2)e^{-\lambda_2 t}}{(\lambda_1 - k_{21} - k_{12})e^{-\lambda_1 t} + (k_{21} - \lambda_2 + k_{12})e^{-\lambda_2 t}} \tag{2.179}$$

In the postdistributive phase (i.e., as $e^{-\lambda_1 t}$ approaches zero),

$$f_c = f_c^* = \frac{(k_{21} - \lambda_2)e^{-\lambda_2 t}}{(k_{21} - \lambda_2 + k_{12})e^{-\lambda_2 t}} \tag{2.180}$$

which readily reduces to

$$f_c^* = \frac{k_{21} - \lambda_2}{k_{21} + k_{12} - \lambda_2} \tag{2.181}$$

Therefore, in the postdistributive phase the fraction of drug in the body that is in the central compartment is a constant, f_c^*.

The rate of change in the amount of drug in the body (dX/dt) equals the sum of the rates of change in the amounts of drug in the central and peripheral body compartments:

$$\frac{dX}{dt} = \frac{dX_c}{dt} + \frac{dX_p}{dt} \tag{2.182}$$

The differential equations for dX_c/dt and dX_p/dt based on the model in Fig. 2.3 are

$$\frac{dX_c}{dt} = k_{21}X_p - k_{12}X_c - k_{10}X_c \tag{2.183}$$

and

$$\frac{dX_p}{dt} = k_{12}X_c - k_{21}X_p \tag{2.184}$$

respectively. Substitution for dX_c/dt and dX_p/dt, according to (2.183) and (2.184), respectively, in (2.182) yields

$$\frac{dX}{dt} = k_{21}X_p - k_{12}X_c - k_{10}X_c + k_{12}X_c - k_{21}X_p \tag{2.185}$$

which readily reduces to

$$\frac{dX}{dt} = -k_{10}X_c \tag{2.186}$$

By substituting for X_c, according to (2.4) with n = 2, in (2.186), the following equation is obtained:

$$\frac{dX}{dt} = -k_{10}\left[\frac{X_0(\lambda_1 - k_{21})}{\lambda_1 - \lambda_2} e^{-\lambda_1 t} + \frac{X_0(k_{21} - \lambda_2)}{\lambda_1 - \lambda_2} e^{-\lambda_2 t}\right] \tag{2.187}$$

Some time after administration $e^{-\lambda_1 t}$ approaches zero (i.e., during the postdistributive phase) and (2.187) reduces to

$$\frac{dX}{dt} = -k_{10}\frac{X_0(k_{21} - \lambda_2)}{\lambda_1 - \lambda_2} e^{-\lambda_2 t} \tag{2.188}$$

Rearrangement and expansion of (2.188) yields

$$\frac{dX}{dt} = -X_0\frac{k_{10}k_{21} - k_{10}\lambda_2}{\lambda_1 - \lambda_2} e^{-\lambda_2 t} \tag{2.189}$$

Recognizing that $k_{10}k_{21} = \lambda_1\lambda_2$ [Eq. (2.100)], substituting $\lambda_1\lambda_2$ for $k_{10}k_{21}$ in (2.189), and rearranging the terms produces the relationship

$$\frac{dX}{dt} = -\lambda_2 \left[\frac{X_0(\lambda_1 - k_{10})}{\lambda_1 - \lambda_2} e^{-\lambda_2 t} \right] \tag{2.190}$$

It can now be shown that the term in brackets equals the amount of drug in the body during the postdistributive phase. The amount of drug in the body (X) is equal to $X_c + X_p$ [Eq. (2.175)] and is given by the denominator of (2.177):

$$X = X_0 \frac{E_2 - \lambda_1}{\lambda_2 - \lambda_1} e^{-\lambda_1 t} + X_0 \frac{E_2 - \lambda_2}{\lambda_1 - \lambda_2} e^{-\lambda_2 t} + X_0 \frac{k_{12}(E_2 - \lambda_1)}{(E_2 - \lambda_1)(\lambda_2 - \lambda_1)} e^{-\lambda_1 t} + X_0 \frac{k_{12}(E_2 - \lambda_2)}{(E_2 - \lambda_2)(\lambda_1 - \lambda_2)} e^{-\lambda_2 t} \tag{2.191}$$

Solving for X in the postdistributive phase (i.e., $e^{-\lambda_1 t} \to 0$), canceling the common term $E_2 - \lambda_2$, and substituting k_{21} for E_2 yields the following equation for the amount of drug in the body during the terminal exponential phase:

$$X = \frac{X_0(k_{21} - \lambda_2 + k_{12})}{\lambda_1 - \lambda_2} e^{-\lambda_2 t} \tag{2.192}$$

Rearrangement of (2.99) gives the expression

$$k_{21} - \lambda_2 + k_{12} = \lambda_1 - k_{10} \tag{2.193}$$

Therefore,

$$X = \frac{X_0(\lambda_1 - k_{10})}{\lambda_1 - \lambda_2} e^{-\lambda_2 t} \tag{2.194}$$

Substituting X for $X_0(\lambda_1 - k_{10})e^{-\lambda_2 t}/(\lambda_1 - \lambda_2)$, as given by (2.194), into (2.190) yields the following equation for the rate of change of drug levels in the body during the postdistributive phase:

$$\frac{dX}{dt} = -\lambda_2 X \tag{2.195}$$

Since $X_c = f_c X$ [Eq. (2.174)], (2.186) may be expressed as

$$\frac{dX}{dt} = -k_{10} f_c X \tag{2.196}$$

In the postdistributive phase,

$$\frac{dX}{dt} = -k_{10} f_c^* X \tag{2.197}$$

where f_c^* is given by (2.181). By comparing (2.196) and (2.197), one concludes that

$$\lambda_2 = f_c^* k_{10} \tag{2.198}$$

It is clear from this equation that λ_2 is a function of both elimination (k_{10}) and distribution.

The dependence of λ_n or β on both distribution and elimination may be demonstrated in a different manner. It has been shown previously that $\lambda_1 + \lambda_2 = k_{12} + k_{21} + k_{10}$ [Eq. (2.99)] and $\lambda_1\lambda_2 = k_{21}k_{10}$ [Eq. (2.100)]. Solving (2.100) for λ_1 yields

$$\lambda_1 = \frac{k_{21}k_{10}}{\lambda_2} \tag{2.199}$$

Substituting this value for λ_1 into (2.99), multiplying each side of the equation by λ_2, and rearranging terms results in the quadratic equation

$$\lambda_2^2 - (k_{12} + k_{21} + k_{10})\lambda_2 + k_{21}k_{10} = 0 \tag{2.200}$$

which is of the form

$$ax^2 + bx + c = 0 \tag{2.201}$$

The general solution of (2.201) is

$$x = \frac{-b \pm \sqrt{b^2 - 4ac}}{2a} \tag{2.162}$$

Therefore,

$$\lambda_2 = \frac{1}{2}\left[(k_{12} + k_{21} + k_{10}) - \sqrt{(k_{12} + k_{21} + k_{10})^2 - 4k_{21}k_{10}}\right] \tag{2.202}$$

The sign preceding the square root term is negative rather than positive since λ_1 has been assumed to be greater than λ_2. It can be readily demonstrated that the equation for λ_1 is identical to (2.202) except that a positive sign precedes the square root term.

The constant k_{10} is the elimination rate constant from the central compartment, and λ_2 reflects drug elimination from the body. The biologic half-life $t_{1/2}$ of a drug is calculated from λ_2 [Eq. (2.11)] rather than from k_{10}. Although λ_2 and half-life are hybrid parameters, they are among the most important functional pharmacokinetic parameters.

If, because of insufficient data, the plasma concentration of a drug with multicompartment characteristics after rapid intravenous injection show only the terminal exponential phase, what is actually the

λ_2 value will appear to be the elimination rate constant K in a one-compartment model.

Volume of Distribution and Clearance

The apparent volume of distribution is a useful pharmacokinetic parameter that relates the plasma or serum concentration of a drug to the total amount of drug in the body. Despite its name, this parameter usually has no direct physiologic meaning and does not refer to a real volume. However, it does provide some insight into the extent of extravascular distribution of a drug; that is, the greater the volume of distribution, the more extensive the extravascular distribution of a drug, and hence the lower the plasma or serum concentration of a drug for a given amount of drug in the body. For a drug with a plasma concentration versus time profile that can be adequately described by a single exponential following an intravenous bolus dose, there is only one volume of distribution parameter. There may be several volume parameters, however, for a drug whose disposition requires a multiexponential equation for its description. One volume term that has been mentioned in this chapter is V_c, the apparent volume of the central compartment. This parameter relates the drug concentration in the plasma to the amount of drug in the central compartment, and can be readily determined from the relationship given by (2.15)

$$V_c = \frac{X_0}{\sum_{\ell=1}^{n} A_\ell}$$

where X_0 is the intravenous dose and $\sum_{\ell=1}^{n} A_\ell$ is the sum of the n zero-time intercepts that would be obtained by applying the method of residuals to a plasma concentration-time curve after intravenous administration of a drug that requires n exponentials to characterize it. By assuming that a constant ratio of drug concentrations in the various tissues and fluids of the central compartment exists, V_c can be employed to estimate the amount of drug in the central compartment at any time regardless of the complexity of the model required to describe the time course of drug in the plasma.

An additional volume parameter in multicompartment systems is V_β. This parameter relates plasma concentration to amount of drug in the body during the terminal exponential phase of a plasma concentration versus time curve. The fraction of drug in the body which is in the central compartment during this terminal exponential phase, f_c^*, is given by

$$f_c^* = \frac{X_c}{X} \qquad (2.203)$$

$V_\beta C$ can be substituted for X in (2.203) since by definition $X = V_\beta C$ during the terminal phase. Therefore,

$$f_c^* = \frac{X_c}{V_\beta C} \tag{2.204}$$

Substitution of $V_c C$ for X_c, according to (2.5), in (2.204) and cancellation of the common term yields

$$f_c^* = \frac{V_c}{V_\beta} \tag{2.205}$$

Equation (2.198) can be rearranged to give

$$f_c^* = \frac{\lambda_2}{k_{10}} \tag{2.206}$$

where k_{10} is the first-order elimination rate constant and λ_2 is the disposition rate constant associated with the terminal exponential phase of a biexponential plasma concentration versus time curve. Although (2.198) was derived assuming that n = 2, a similar relationship would have resulted regardless of the number of exponentials required to describe a plasma concentration versus time curve provided that elimination is assumed to occur from the central compartment. Therefore, (2.206) can be written as

$$f_c^* = \frac{\lambda_n}{k_{10}} \tag{2.207}$$

By comparing (2.205) and (2.207), it becomes readily apparent that

$$\frac{V_c}{V_\beta} = \frac{\lambda_n}{k_{10}} \tag{2.208}$$

Rearrangement of (2.208) provides one approach for the determination of V_β:

$$V_\beta = \frac{V_c k_{10}}{\lambda_n} \tag{2.209}$$

Solving Eqs. (2.38) ($k_e' V_c = X_u^\infty / AUC$) and (2.121) ($k_e' = X_u^\infty k_{10} / X_0$) for X_u^∞ / k_e' yields

$$\frac{X_u^\infty}{k_e'} = V_c \cdot AUC \tag{2.210}$$

and

$$\frac{X_u^{\infty}}{k_e'} = \frac{X_0}{k_{10}} \tag{2.211}$$

Equating the right-hand sides of (2.210) and (2.211) and rearranging the resulting expression gives

$$V_c k_{10} = \frac{X_0}{AUC} \tag{2.212}$$

Substitution of this value of $V_c k_{10}$ for $V_c k_{10}$ in (2.209) results in the following general equation for the determination of V_β:

$$V_\beta = \frac{X_0}{\lambda_n \cdot AUC} \tag{2.213}$$

where AUC is the total area under the plasma concentration versus time curve. This method of calculating V_β is independent of the number of exponentials required to describe a plasma concentration versus time curve, and is analogous to the equation used to calculate volume of distribution in a one-compartment model: Eq. (1.35) ($V = X_0/K \cdot AUC$), where K is the first-order elimination rate constant of a drug. As mentioned previously, V_β, as determined by (2.213), can be used to determine the amount of drug in the body during the terminal exponential phase of a plasma concentration-time curve provided that elimination occurs only from the central compartment. Equation (2.213) can also be used to calculate V_β from intravenous infusion data. When infusion data are employed, X_0 is equal to the product of the infusion rate k_0 and infusion time T (i.e., k_0T), and AUC is the total area under the plasma concentration versus time curve from the time of initiation of the infusion to time infinity after cessation of the infusion.

Methods for the calculation of the clearance Cl_s of a drug using both intravenous bolus and steady-state infusion data were presented earlier in the chapter. The relationships are

$$Cl_s = \frac{X_0}{AUC} \tag{2.43}$$

and

$$Cl_s = \frac{k_0}{C_{ss}} \tag{2.59}$$

where C_{ss} is the steady-state plasma concentration of a drug during an intravenous infusion. Equation (2.213) can be rearranged to yield

$$V_\beta \lambda_n = \frac{X_0}{AUC} \tag{2.214}$$

A comparison of (2.212), (2.214), and (2.43) reveals that

$$Cl_s = V_\beta \lambda_n = V_c k_{10} \tag{2.215}$$

Equation (2.215) can also be used to determine V_β once clearance is known since

$$V_\beta = \frac{Cl_s}{\lambda_n} \tag{2.216}$$

Substituting $0.693/t_{1/2}$ for λ_n [Eq. (2.11)] in (2.216) and solving for $t_{1/2}$ gives

$$t_{1/2} = 0.693 \frac{V_\beta}{Cl_s} \tag{2.217}$$

which again illustrates the dependence of $t_{1/2}$ on both the distribution and elimination characteristics of a drug.

An additional volume parameter and probably the most useful volume term to describe the apparent distribution space in a multicompartment system is V_{ss}, the apparent volume of distribution at steady state. This parameter was initially derived by Riggs [25], who equated it to the sum of the apparent volumes of the central and peripheral compartments. As its name implies, V_{ss} relates the amount of drug in the body to the drug concentration in the plasma at steady state during repetitive dosing or constant rate infusion:

$$X_{ss} = V_{ss} C_{ss} \tag{2.218}$$

and

$$\bar{X} = V_{ss} \bar{C} \tag{2.219}$$

where X_{ss} and C_{ss} are the amount of drug in the body and plasma concentration of drug at steady state, respectively, during constant rate infusion, and $\bar{X}$ and $\bar{C}$ are the "average" amount of drug in the body and plasma concentration of drug at steady state, respectively, during repetitive dosing.

Rearrangement of (2.219) yields the following relationship for V_{ss}:

$$V_{ss} = \frac{\bar{X}}{\bar{C}} \tag{2.220}$$

The amount of drug in the body at any time t after a single intravenous bolus dose in a multicompartment system is given by the difference be-

tween the administered dose X_0 and the amount eliminated up to that time, $(X_E)_0^t$:

$$X = X_0 - (X_E)_0^t \tag{2.221}$$

Solving (2.41) for dX_E/dt and integrating the resulting expression from time zero to t gives

$$(X_E)_0^t = Cl_s \int_0^t C\, dt \tag{2.222}$$

where Cl_s is clearance and $\int_0^t C\, dt$ is the area under the plasma concentration time curve described by (2.7). Substitution for $(X_E)_0^t$ in (2.221) according to (2.222) yields

$$X = X_0 - Cl_s \int_0^t C\, dt \tag{2.223}$$

Integrating (2.7) from time zero to t and substituting the resulting expression for $\int_0^t C\, dt$ in (2.223) gives

$$X = X_0 - Cl_s \sum_{\ell=1}^{n} \frac{A_\ell}{\lambda_\ell}(1 - e^{-\lambda_\ell t}) \tag{2.224}$$

The clearance of a drug is equal to the ratio of the intravenous dose to the total area under the drug concentration in the plasma versus time curve [i.e., $Cl_s = X_0/AUC$; Eq. (2.43)]. Substitution of $\Sigma_{\ell=1}^{n} A_\ell/\lambda_\ell$ for AUC, according to (2.40), in (2.43) yields

$$Cl_s = \frac{X_0}{\sum_{\ell=1}^{n} (A_\ell/\lambda_\ell)} \tag{2.225}$$

This value of Cl_s can then be substituted for Cl_s in (2.224) to give

$$X = X_0 - \frac{X_0 \sum_{\ell=1}^{n} [(A_\ell/\lambda_\ell)(1 - e^{-\lambda_\ell t})]}{\sum_{\ell=1}^{n} (A_\ell/\lambda_\ell)} \tag{2.226}$$

or

$$X = \frac{X_0 \left\{ \sum_{\ell=1}^{n} (A_\ell/\lambda_\ell) - \sum_{\ell=1}^{n} (A_\ell/\lambda_\ell) + \sum_{\ell=1}^{n} [(A_\ell/\lambda_\ell)e^{-\lambda_\ell t}] \right\}}{\sum_{\ell=1}^{n} (A_\ell/\lambda_\ell)} \tag{2.227}$$

On canceling common terms, the following results:

$$X = \frac{X_0 \sum_{\ell=1}^{n} [(A_\ell/\lambda_\ell)e^{-\lambda_\ell t}]}{\sum_{\ell=1}^{n} (A_\ell/\lambda_\ell)} \tag{2.228}$$

To convert the single-dose expression (2.228) to one describing the situation during a dosing interval at steady state, the exponential term in (2.228) is multiplied by $1/(1 - e^{-\lambda_\ell \tau})$, where τ is the dosing interval, which is obtained by setting k_i in the multiple-dosing function equal to λ_ℓ and recognizing that $e^{-N\lambda_\ell \tau}$ approaches zero at steady state (see Appendix B). Therefore,

$$X_{ss} = \frac{X_0 \sum_{\ell=1}^{n} [A_\ell e^{-\lambda_\ell t}/\lambda_\ell(1 - e^{-\lambda_\ell \tau})]}{\sum_{\ell=1}^{n} (A_\ell/\lambda_\ell)} \tag{2.229}$$

where X_{ss} is the amount of drug in the body during a dosing interval at steady state. The average amount of drug in the body at steady state $\bar{X}$ is defined as

$$\bar{X} = \frac{\int_0^\tau X_{ss}\, dt}{\tau} \tag{2.230}$$

Integration of the summation term in the numerator of (2.229) from $t = 0$ to $t = \tau$ yields

$$\int_0^\tau \sum_{\ell=1}^{n} \frac{A_\ell e^{-\lambda_\ell t}}{\lambda_\ell(1 - e^{-\lambda_\ell \tau})} = \sum_{\ell=1}^{n} \frac{-A_\ell e^{-\lambda_\ell t}}{\lambda_\ell^2(1 - e^{-\lambda_\ell \tau})} \Bigg|_0^\tau = \sum_{\ell=1}^{n} \frac{A_\ell}{\lambda_\ell^2} \tag{2.231}$$

It follows that

$$\overline{X} = \frac{X_0 \sum_{\ell=1}^{n} (A_\ell/\lambda_\ell^2)}{\tau \sum_{\ell=1}^{n} (A_\ell/\lambda_\ell)} \tag{2.232}$$

The average concentration of drug in the plasma at steady state $\overline{C}$ is given by

$$\overline{C} = \frac{\int_0^\tau C_{ss}\, dt}{\tau} \tag{3.25}$$

Substitution of $\sum_{\ell=1}^{n} A_\ell/\lambda_\ell$ for $\int_0^\tau C_{ss}\, dt$, according to (3.26), in (3.25) gives

$$\overline{C} = \frac{\sum_{\ell=1}^{n} (A_\ell/\lambda_\ell)}{\tau} \tag{2.233}$$

The values of $\overline{X}$ and $\overline{C}$ as given by (2.232) and (2.233), respectively, can be substituted in (2.220) to yield

$$V_{ss} = \frac{X_0 \sum_{\ell=1}^{n} (A_\ell/\lambda_\ell^2)}{\left[\sum_{\ell=1}^{n} (A_\ell/\lambda_\ell)\right]^2} = \frac{X_0 \sum_{\ell=1}^{n} (A_\ell/\lambda_\ell^2)}{(AUC)^2} \tag{2.234}$$

Therefore, once the estimates of A_ℓ and λ_ℓ are obtained from a fit of plasma concentration versus time data, V_{ss} can be readily estimated employing (2.234).

Although clearance and volume of distribution parameters have been discussed in this section, a more detailed presentation of their physiologic significance may be found in Chaps. 8 and 5, respectively.

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